HANDBOOK OF HETEROGENEOUS CATALYTIC HYDROGENATION FOR ORGANIC SYNTHESIS

SHIGEO NISHIMURA
Professor Emeritus
Tokyo University of Agriculture and Technology

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PREFACE

Catalytic hydrogenation is undoubtedly the most useful and widely applicable method for the reduction of chemical substances, and has found numerous applications in organic synthesis in research laboratories and industrial processes. Almost all catalytic hydrogenations have been accomplished using heterogeneous catalysts since the earliest stages. Homogeneous catalysts have been further developed and have extended the scope of catalytic hydrogenation, in particular, for highly selective transformations. However, heterogeneous catalysts today continue to have many advantages over homogeneous catalysts, such as in the stability of catalyst, ease of separation of product from catalyst, a wide range of applicable reaction conditions, and high catalytic ability for the hydrogenation of hard-to-reduce functional groups such as aromatic nuclei and sterically hindered unsaturations and for the hydrogenolyses of carbon–carbon bonds. Also, many examples are included here where highly selective hydrogenations have been achieved over heterogeneous catalysts, typically in collaboration with effective additives, acids and bases, and solvents.

Examples of the hydrogenation of various functional groups and reaction pathways are illustrated in numerous equations and schemes in order to help the reader easily understand the reactions. In general, the reactions labeled as equations are described with experimental details to enable the user to choose a pertinent catalyst in a proper ratio to the substrate, a suitable solvent, and suitable reaction conditions for hydrogenation to be completed within a reasonable time. The reactions labeled as schemes will be helpful for better understanding reaction pathways as well as the selectivity of catalysts, although the difference between equations and schemes is not strict. Simple reactions are sometimes described in equations without experimental details. Comparable data are included in more than 100 tables, and will help the user understand the effects of various factors on the rate and/or selectivity, including the structure of compounds, the nature of catalysts and supports, and the nature of solvents and additives. A considerable number of experimental results not yet published by the author and coworkers can be found in this Handbook.

This book is intended primarily to provide experimental guidelines for organic syntheses. However, in fundamental hydrogenations, mechanistic aspects (to a limited extent) are also included. The hydrogenations of industrial importance have been described with adequate experimental and mechanistic details.

The references quoted here are by no means comprehensive. In general, those that seem to be related to basic or selective hydrogenations have been selected.

I am grateful to the authors of many excellent books to which I have referred during preparation of this book. These books are listed at the end of chapters under "General Bibliography."

I wish to express my thanks to the libraries and staff of The Institute of Physical and Chemical Research, Wako, Saitama and of Tokyo University of Pharmacy and Life Science, Hachioji, Tokyo. I acknowledge John Wiley and Sons, Inc. and their editorial staff for their cordial guidance and assistance in publishing this book. I thank Professor Emeritus Michio Shiota of Ochanomizu University and Professor Yuzuru Takagi of Nihon University for their helpful discussions. Special thanks are due to my three children who provided me with a new model personal computer with a TFT-LC display for preparing the manuscript and to my wife Yasuko, who had continuously encouraged and supported me in preparing and publishing this book until her death on November 28, 1999.

SHIGEO NISHIMURA

Hachioji, Tokyo

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CHAPTER 1

Hydrogenation Catalysts

Heterogeneous transition metal catalysts for hydrogenation are usually employed in the states of metals, oxides, or sulfides that are either unsupported or supported. The physical form of a catalyst suitable for a particular hydrogenation is determined primarily by the type of reactors, such as fixed-bed, fluidized-bed, or batch reactor. For industrial purposes, unsupported catalysts are seldom employed since supported catalysts have many advantages over unsupported catalysts. One exception to this is Raney-type catalysts, which are effectively employed in industrial hydrogenations in unsupported states. In general, use of a support allows the active component to have a larger exposed surface area, which is particularly important in those cases where a high temperature is required to activate the active component. At that temperature, it tends to lose its high activity during the activation process, such as in the reduction of nickel oxides with hydrogen, or where the active component is very expensive as are the cases with platinum group metals. Unsupported catalysts have been widely employed in laboratory use, especially in hydrogenations using platinum metals. Finely divided platinum metals, often referred to as "blacks," have been preferred for hydrogenations on very small scale and have played an important role in the transformation or the determination of structure of natural products that are available only in small quantities. The effect of an additive or impurity appears to be more sensitive for unsupported blacks than for supported catalysts. This is also in line with the observations that supported catalysts are usually more resistant to poisons than are unsupported catalysts.[1] Noble metal catalysts have also been employed in colloidal forms and are often recognized to be more active and/or selective than the usual metal blacks, although colloidal catalysts may suffer from the disadvantages due to their instability and the difficulty in the separation of product from catalyst. It is often argued that the high selectivity of a colloidal catalyst results from its high degree of dispersion. However, the nature of colloidal catalysts may have been modified with protective colloids or with the substances resulting from reducing agents. Examples are known where selectivity as high as or even higher than that with a colloidal catalyst have been obtained by mere addition of an appropriate catalyst poison to a metal black or by poisoning supported catalysts (see, e.g., Chapter 3, Ref. 76 and Fig. 4.1). Supported catalysts may be prepared by a variety of methods, depending on the nature of active components as well as the characteristics of carriers. An active component may be incorporated with a carrier in various ways, such as, by decomposition, impregnation, precipitation, coprecipitation, adsorption, or ion exchange. Both low- and high-surface-area materials are employed as carriers. Some characteristics of commonly used supporting materials are summarized in Table 1.1. Besides these, the carbonates and sulfates of alkaline-earth elements, such as cal-

TABLE 1.1 Characteristics of Commonly Used Carriers

Carrier	Specific Surface Area ($m^2 \cdot g^{-1}$)	Pore Volume ($ml \cdot g^{-1}$)	Average Pore Diameter (nm)
α–Al_2O_3[a]	0.1–5	—	500–2,000
Kieselguhr[a]	2–35	1–5	>100
Activated Al_2O_3[b]	100–350	0.4	4–9
SiO_2–Al_2O_3[b]	200–600	0.5–0.7	3–15
SiO_2[b]	400–800	0.4–0.8	2–8
Zeolite[b]	400–900	0.08–0.2	0.3–0.8
Activated carbon[b]	800–1200	0.2–2.0	1–4

[a]These are classified usually as low-area carriers.
[b]These are classified usually as high-area, porous carriers having surface areas in exceeding ~50 m^2/g, porosities greater than ~0.2 ml/g, and pore sizes less than 20 nm (Innes, W. B. in *Catalysis*; Emmett, P. H., Ed.; Reinhold: New York, 1954; Vol. 1, p 245).

cium carbonate and barium sulfate, are often used as carriers for the preparation of palladium catalysts that are moderately active but more selective than those supported on carbon. A more recent technique employs a procedure often called *chemical mixing*, where, for example, the metal alkoxide of an active component together with that of a supporting component, such as aluminum alkoxide or tetraalkyl orthosilicate, is hydrolyzed to give a supported catalyst with uniformly dispersed metal particles.[2,3] Examples are seen in the preparations of Ag–Cd–Zn–SiO_2 catalyst for selective hydrogenation of acrolein to allyl alcohol (see Section 5.2) and Ru–SiO_2 catalysts for selective hydrogenation of benzene to cyclohexene (see Section 11.1.1).

1.1 NICKEL CATALYSTS

The preparation and activation of unsupported nickel catalysts have been studied by numerous investigators.[4] As originally studied by Sabatier and co-workers,[5] nickel oxide free from chlorine or sulfur was obtained by calcination of nickel nitrate. The temperature at which nickel oxide is reduced by hydrogen greatly affects the activity of the resulting catalyst. There is a considerable temperature difference between the commencement and the completion of the reduction. According to Senderens and Aboulenc,[6] reduction commences at about 300°C but the temperature must be raised to 420°C for complete reduction, although insufficiently reduced nickel oxides are usually more active than completely reduced ones. On the other hand, Sabatier and Espil observed that the nickel catalyst from nickel oxide reduced at 500°C and kept for 8 h at temperatures between 500 and 700°C still maintained its ability to hydrogenate the benzene ring.[7] Benton and Emmett found that, in contrast to ferric oxide, the reduction of nickel oxide was autocatalytic and that the higher the temperature of preparation, the higher the temperature necessary to obtain a useful rate of reduction, and the less the autocatalytic effect.[8] Although the hydroxide of nickel may be reduced at lower temperatures than nickel oxide,[6] the resulting catalyst is not only unduly sen-

sitive but also difficult to control. When applied to phenol, it tends to produce cyclohexane instead of cyclohaxanol.[9] Although supported catalysts may require a higher temperature for activation with hydrogen than unsupported ones, they are much more stable and can retain greater activity even at higher temperatures. Thus, reduced nickel is usually employed with a support such as kieselguhr for practical uses.

Various active nickel catalysts obtained not via reduction of nickel oxide with hydrogen have been described in the literature. Among these are the catalysts obtained by the decomposition of nickel carbonyl;[10] by thermal decomposition of nickel formate or oxalate;[11] by treating Ni–Si alloy or, more commonly, Ni–Al alloy with caustic alkali (or with heated water or steam) (Raney Ni);[12] by reducing nickel salts with a more electropositive metal,[13] particularly by zinc dust followed by activation with an alkali or acid (Urushibara Ni);[14–16] and by reducing nickel salts with sodium borohydride (Ni boride catalyst)[17–19] or other reducing agents.[20–24]

1.1.1 Reduced Nickel

Many investigators, in particular, Kelber,[25] Armstrong and Hilditch,[26] and Gauger and Taylor,[27] have recognized that nickel oxide when supported on kieselguhr gives much more active catalysts than an unsupported one, although the reduction temperature required for the supported oxide (350–500°C) is considerably higher than that required for the unsupported oxide (250–300°C). Gauger and Taylor studied the adsorptive capacity of gases on unsupported and supported nickel catalysts prepared by reducing the nickel oxide obtained by calcining nickel nitrate at 300°C. The adsorptive capacity of hydrogen per gram of nickel was increased almost 10-fold when supported on kieselguhr (10% Ni), although hydrogen reduction for more than one week at 350°C or 40 min at 500°C was required for the supported catalysts, compared to 300°C or rapid reduction at 350°C for the unsupported oxide. Adkins and co-workers[28–30] studied in details the conditions for the preparation of an active Ni–kieselguhr catalyst by the precipitation method, which gave much better catalysts than those deposited by decomposing nickel nitrate on kieselguhr. Their results led to the conclusions that (1) nickel sulfate, chloride, acetate, or nitrate may be used as the source of nickel, provided the catalyst is thoroughly washed, although the nitrate is preferred because of the easiness in obtaining the catalyst free of halide or sulfate (industrially, however, the sulfate is used by far in the largest quantities because it is the cheapest and most generally available[31]); (2) for the carbonate catalysts, the addition of the precipitant to the soluble nickel compound on kieselguhr gives better results than if the reverse order is followed i.e., the addition of the soluble nickel compound on kieselguhr to the precipitant; and (3) with potassium hydroxide as the precipitant, the resulting catalyst is somewhat inferior to the carbonate catalysts prepared with sodium carbonate or bicarbonate, and ammonium carbonate is in general the most satisfactory precipitant. According to Adkins, the advantages of using ammonium carbonate are due in part to the ease with which ammonium salts are removed, and in part to excellent agitation of the reaction mixture due to the evolution of carbon dioxide.[32] Further, with ammonium carbonate as the precipitant it makes little difference by the order of the addition of the reagents. The effect of time and temperature on the extent of reduction and catalytic

TABLE 1.2 Effect of Time and Temperature upon Extent of Reduction and Activity of Ni–Kieselguhr[a]

	Reduction			Time for Reduction of Acetone[b] (min)	
Catalyst	Temperature (°C)	Time (min)	Metallic Ni (%)	Middle 60%	100%
Kieselguhr–$Ni(NO_3)_2$ added to Na_2CO_3 solution (12.6% Ni)	450	30		26	52
	525	30	—	22	55
	525	45	—	17	35
	450	60	5.14	23	39
	500	60[c]	7.66	10	16
	550	60	—	16	26
	450	90	—	17	25
Na_2CO_3 solution added to kieselguhr–$Ni(NO_3)_2$ (12.5% Ni)	450	30	—	20	40
	525	30	—	21	59
	525	45	—	17	35
	450	60	5.14	21	47
	500	60[c]	7.38	18	30
	550	60	—	21	85
	450	90	—	29	40
$NaHCO_3$ solution added to kieselguhr–$Ni(NO_3)_2$ (13.6% Ni)	450	30	—	86	150
	525	30	—	24	45
	525	45	—	44	74
	450	60	9.88	11	30
	500	60[c]	10.2	21	60
	550	60	—	103	160
	450	90	—	10	25
Kieselguhr–$Ni(NO_3)_2$ added to $(NH_4)_2CO_3$ solution (14.9% Ni)	450	60	10.4	10	23
	500	60	10.3	25	55
$(NH_4)_2CO_3$ solution added to kieselguhr–$Ni(NO_3)_2$ (13.6% Ni)	450	60	7.85	10	20
	550	60	7.95	19	45

[a]Data of Covert, L. W.; Connor, R.; Adkins, H. *J. Am. Chem. Soc.* **1932**, *54*, 1651. Reprinted with permission from American Chemical Society.
[b]1.0 mol of acetone, 2 g of catalyst, 125°C, 12.7 MPa H_2.
[c]The content of metallic nickel was not materially increased by longer times for reduction even up to 5 h.

activity of the resulting catalyst is summarized in Table 1.2. It is seen that higher temperatures and longer times are required for the reduction of the sodium carbonate catalysts than for the bicarbonate or ammonium carbonate catalysts. Temperatures above 500°C and times exceeding 60 min are definitely injurious. It appears that the reduction at 450°C for 60 min is sufficient for the bicarbonate or ammonium carbonate catalysts. For all the catalysts there is a considerable portion of the nickel that was not reduced even after several hours, but this portion is greater for the sodium carbonate catalysts. The most satisfactory procedure for the preparation of a Ni–kieselguhr catalyst recommended by Covert et al. with use of ammonium carbonate as a precipitant is described below.

Ni–Kieselguhr (with Ammonium Carbonate).[30] In this procedure 58 g of nickel nitrate hexahydrate [$Ni(NO_3)_2 \cdot 6H_2O$], dissolved in 80 ml of distilled water, is ground for 30–60 min in a mortar with 50 g of acid washed kieselguhr (e.g., Johns–Manville "Filter-Cel") until the mixture is apparently homogeneous and flowed as freely as a heavy lubricating oil. It is then slowly added to a solution prepared from 34 g of ammonium carbonate monohydrate [$(NH_4)_2CO_3 \cdot H_2O$] and 200 ml of distilled water. The resulting mixture is filtered with suction, washed with 100 ml of water in two portions, and dried overnight at 110°C. The yield is 66 g. Just before use, 2–6 g of the product so obtained is reduced for 1 h at 450°C in a stream of hydrogen passing over the catalyst at a rate of 10–15 ml/min. The catalyst is then cooled to room temperature and transferred in a stream of hydrogen to the reaction vessel, which has been filled with carbon dioxide.

Covert et al. tested various promoters such as Cu, Zn, Cr, Mo, Ba, Mn, Ce, Fe, Co, B, Ag, Mg, Sn, and Si in the hydrogenation of acetone, the diethyl acetal of furfural, and toluene, when incorporated with nickel. The effects of the promoters depended on the substrate; an element that promoted the hydrogenation of one compound might retard that of another. Further, it appeared that none of the promoters tested greatly increased the activity of the nickel catalyst,[30] although various coprecipitated promoters such as Cu, Cr, Co, Th, and Zr have been referred to in the literature, especially in patents.[33] The effect of copper, in particular, has been the subject of a considerable body of investigations from both practical and academic viewpoints.[34–36] Basic compounds of copper undergo reduction to metal at a lower temperature than do the corresponding nickel compounds, and the reduced copper may catalyze the reduction of nickel compounds. Thus nickel hydroxide or carbonate coprecipitated with copper compounds may be reduced at a low temperature of 200°C, which allows "wet reduction" at normal oil-hardening temperatures (~180°C)[37] to give wet-reduced nickel–copper catalysts which were widely used in the past.[33]

Scaros et al. activated a commercially available Ni–Al_2O_3 catalyst (58–65% Ni) by adding a slurry of potassium borohydride in ammonium hydroxide and methanol to a stirred THF (terahydrofuran) solution of the substrate and suspended Ni–Al_2O_3.[38] The resulting catalyst can be employed at pressures as low as 0.34 MPa and temperatures as low as 50°C, the conditions comparable to those for Raney Ni, and has the distinct advantage of being nonpyrophoric, a property required particularly in large-scale hydrogenation. Thus, over this catalyst, the hydrogenation of the alkyne ester, $RC{\equiv}CCO_2Me$, to the corresponding alkyl ester and the hydrogenation of adiponitrile to 1,6-hexanediamine were accomplished at 50°C and 0.34 MPa H_2 within reaction times comparable to those required for the hydrogenations with Raney Ni. The Ni–Al_2O_3 catalyst can also be activated externally and stored for up to 13 weeks in water or 2-methoxyethanol.

1.1.2 Nickel from Nickel Formate

When nickel formate, which usually occurs as a dihydrate, is heated, it first loses water at about 140°C, and then starts to decompose at 210°C to give a finely divided nickel catalyst with evolution of a gas mixture composed mainly of carbon dioxide, hydro-

gen, and water.[31] The main reaction is expressed as in eq. 1.1. However, some of nickel formate may be decomposed according to the reaction shown in eq. 1.2.[39–41]

$$Ni(HCOO)_2 \cdot 2H_2O \rightarrow Ni + 2CO_2 + H_2 + 2H_2O \quad (1.1)$$

$$Ni(HCOO)_2 \cdot 2H_2O \rightarrow Ni + CO + CO_2 + 3H_2O \quad (1.2)$$

Thus an active nickel catalyst may be prepared simply by heating the formate in oil at around 240°C for about 1 h; this method has been employed in the oil-hardening industry for the preparation of a wet-reduced catalyst,[42] although the decomposition temperature is too high for normal oil-hardening and the catalyst may not be prepared directly in a hydrogenation tank, particularly for edible purposes. Nickel formate is prepared by the reaction between nickel sulfate and sodium formate,[43] or the direct reaction of basic nickel carbonate[44] or nickel hydroxide with formic acid.[31]

Allison et al. prepared the catalyst by decomposing nickel formate in a paraffin–paraffin oil mixture in a vacuum of a water-stream pump.[45] The nickel catalyst thus prepared was not pyrophoric, not sensitive to air and chloride, and showed excellent catalytic properties in the hydrogenation of aqueous solutions of aromatic nitro compounds such as the sodium salts of *m*-nitrobenzenesulfonic acid, *o*-nitrobenzoic acid, and *p*-nitrophenol at pH 5–6. Sasa prepared an active nickel catalyst for the hydrogenation of phenol by decomposing nickel formate in boiling biphenyl [boiling point (bp) 252°C], diphenyl ether (bp 255°C), or a mixture of them (see eq. 11.12).[42]

Ni Catalyst from Ni Formate (by Wurster) (Wet Reduction of Nickel Formate for Oil Hardening).[42] A mixture of 4 parts oil and 1 part nickel formate is heated steadily to about 185°C at atmospheric pressure. At 150°C the initial reaction begins, and at this point or sooner hydrogen gas is introduced. The reaction becomes active at 190°C with the evolution of steam from the water of crystallization. The temperature holds steady for about 30 min until the moisture is driven off and then rises rapidly to 240°C. It is necessary to hold the charge at 240°C, or a few degrees higher, for 30 min–1 h to complete the reaction. The final oil–nickel mixture contains approximately 7% Ni. With equal weights of oil and nickel formate, the final oil–nickel mixture contains approximately 23% Ni.

Ni Catalyst from Ni Formate (by Allisson et al.)[45] In this method 100 g of nickel formate with 100 g of paraffin and 20 g of paraffin oil are heated in a vacuum of water-stream pump. At 170–180°C the water of crystallization is evolved out first (in ~1 h). About 4 h at 245–255°C is required for complete decomposition. The end of the decomposition can best be found by the pressure drop to ~20 mmHg. The still hot mass is poured on a plate; after solidification, the upper paraffin layer is removed as much as possible. The remaining deep black mass is washed with hot water until most of the paraffin is removed off with melt; the remaining powder is washed with alcohol, and then many times with petroleum ether until no paraffin remains.

Ni Catalyst from Ni Formate (by Sasa).[41] A mixture of 2.6 g of nickel formate dihydrate (0.81 g Ni) and 20 g of freshly distilled diphenyl ether (or biphenyl or a mixture of diphenyl ether and biphenyl) is heated under stirring. The water of crystallization is removed with diphenyl ether. At 250°C, when diphenyl ether starts to boil, the mixture becomes black. After the decomposition for 2 h in boiling diphenyl ether, the nickel catalyst is filtered off at 40–50°C. The catalyst may be used immediately or after washing with alcohol or benzene.

Nickel oxalate, similarly to nickel formate, decomposes to give finely divided nickel powder with the liberation of carbon dioxide containing a trace of carbon monoxide at about 200°C. However, it has not been widely used industrially because of the higher cost of the oxalate.[31]

1.1.3 Raney Nickel

In 1925 and 1927 Raney patented a new method of preparation of an active catalyst from an alloy of a catalytic metal with a substance that may be dissolved by a solvent that will not attack the catalytic metal. First a nickel–silicon alloy was treated with aqueous sodium hydroxide to produce a pyrophoric nickel catalyst. Soon later, in 1927, the method was improved by treating a nickel–aluminum alloy with sodium hydroxide solution because the preparation and the pulverization of the aluminum alloy were easier. Some of most commonly used proportions of nickel and aluminum for the alloy are 50% Ni–50% Al, 42% Ni–58% Al, and 30% Ni–70% Al. The nickel catalyst thus prepared is highly active and now widely known as Raney Nickel, which is today probably the most commonly used nickel catalyst not only for laboratory uses but also for industrial applications.[46]

Although various Ni–Al alloy phases are known, the most important ones that may lead to an active catalyst appear to be Ni_2Al_3 (59% Ni) and $NiAl_3$ (42% Ni). 50% Ni and 42% Ni alloys usually consist of a mixture of the two phases with some other phases. The $NiAl_3$ phase is attacked by caustic alkali much more readily than the Ni_2Al_3 phase. In the original preparation by Covert and Adkins,[47] denoted W-1 Raney Ni, 50% Ni–50% Al alloy was treated (or leached) with an excess amount of about 20% sodium hydroxide solution at the temperature of 115–120°C for 7 h to dissolve off the aluminum from the alloy as completely as possible. In the preparation by Mozingo,[48] denoted W-2 Raney Ni,[49] the digestion was carried out at ~80°C for 8–12 h. Paul and Hilly pointed out that the digestion for such a long period at high temperatures as used in the preparation of W-1 Raney Ni might lead to coating the catalyst with an alumina hydrate formed by hydrolysis of sodium aluminate. In order to depress the formation of the alumina hydrate, they digested the alloy (43% Ni) at 90–100°C for a shorter time after the alloy had been added to 25% sodium hydroxide solution (NaOH = 1 w/w alloy or 1.18 mol/mol Al) in an Erlenmeyer flask cooled with ice. The same digestion process at 90°C for 1 h was repeated twice with addition of the same amount of fresh sodium hydroxide solution each time.[50] Later, Pavlic and Adkins obtained a more active catalyst, particularly for hydrogenations at low temperatures, by lowering the leaching temperature to 50°C and shortening the period of reaction of the alloy with the alkaline solution, and by a more effective method for

washing the catalyst out of contact with air.[51] The time from the beginning of the preparation until the completion of the digestion was reduced from ≥12 h to < 1.5 h. The Raney Ni catalysts thus prepared at low temperatures, denoted W-3,[49,51] W-4,[49,51] W-5,[52] W-6,[52,53] and W-7,[52,53] contain larger amounts of remaining aluminum (~12–13%), but they retain larger amounts of adsorbed hydrogen and show greater activities than do those prepared at higher temperatures. The W-6 Raney Ni, the most active catalyst according to Adkins and Billica, was obtained by leaching the alloy at 50°C, followed by washing the catalyst continuously with water under pressure of hydrogen. The W-7 catalyst is obtained by eliminating a continuous washing process under hydrogen as used in the preparation of W-6 Raney Ni, and contains some remaining alkali, the presence of which may be advantageous in the hydrogenation of ketones, phenols, and nitriles. Some characteristic differences in the preparation of W-1–W-7 catalysts are compared in Table 1.3.

The reaction of Raney alloy with an aqueous sodium hydroxide is highly exothermic, and it is very difficult to put the alloy into the solution within a short time. Accordingly, a catalyst developed not uniformly may result, because the portion of the alloy added at the beginning is treated with the most concentrated sodium hydroxide solution for the longest time while that added last is treated with the most dilute solution for the shortest time. Such lack of uniformity in the degree of development may be disadvantageous for obtaining a catalyst of high activity, especially in the preparation of Raney Ni such as W-6 or W-7 with considerable amounts of remaining aluminum and/or in the development of the alloy containing less than 50% nickel which is known to be more reactive than 50% Ni–50% Al alloy toward sodium hydroxide solution. From this point of view, Nishimura and Urushibara prepared a highly active Raney Ni by adding a sodium hydroxide solution in portions to a 40% nickel alloy suspended in water.[54] In the course of this study, it has been found that the Raney alloy, after being partly leached with a very dilute sodium hydroxide solution, is developed extensively with water, producing a large quantity of bayerite, a crystalline form of aluminum hydroxide. After the reaction with water has subsided, the product of a gray color reacts only very mildly with a concentrated sodium hydroxide solution and it can be added at one time and the digestion continued to remove the bayerite from the catalyst and to complete the development.[55] The Raney Ni thus prepared, denoted T-4, has been found more active than the W-7 catalyst. Use of a larger quantity of sodium hydroxide solution in the preparation of the W-7 catalyst resulted in a less active catalyst, indicating that the 40% Ni alloy was susceptible to overdevelopment to give a catalyst of lower activity even at 50°C. The rapid reaction of Raney alloy with water proceeds through the regeneration of sodium hydroxide, which occurs by the hydrolysis of initially formed sodium aluminate, as suggested by Dirksen and Linden,[56] with formation of alkali-insoluble bayerite (see eq. 1.3).

$$\mathrm{NaAlO_2 + 2H_2O \rightleftharpoons amorphous\ Al(OH)_3 + NaOH}$$

$$\mathrm{amorphous\ Al(OH)_3 \xrightarrow{bayerite} crystalline\ Al(OH)_3\ (bayerite)} \tag{1.3}$$

TABLE 1.3 Conditions for the Preparation of W-1–W-7 Raney Nickel

Raney Ni	Amount of NaOH Used (w/w Alloy[a])	Amount of NaOH Used (mol/mol Al)	Process of Alloy Addition	Digestion	Washing Process	Ref.
W-1	1 + 0.25[b]	1.35	In 2–3 h in a beaker surrounded by ice	At 115–120°C for 4 h and then for 3 h with addition of 2nd portion of NaOH	By decantation 6 times; washings on Buchner filter until neutral to litmus; 3 times with 95% EtOH	47
W-2	1.27	1.71	At 10–25°C in 2 h	At 80°C for 8–12 h	By decantations until neutral to litmus; 3 times with 95% EtOH and 3 times with absolute EtOH	48
W-3	1.28	1.73	All of alloy added at −20°C	As in W-4	As in W-4	49,51
W-4	1.28	1.73	At 50°C in 25–30 min	At 50°C for 50 min	By decantations, followed by continuous washing until neutral to litmus; 3 times with 95% EtOH and 3 times with absolute EtOH	49,51
W-5	1.28	1.73	As in W-4	As in W-4	Washed as in W-6, but without introduction of hydrogen	52
W-6	1.28	1.73	As in W-4	As in W-4	3 times by decantations, followed by continuous washing under hydrogen; 3 times with 95% EtOH and 3 times with absolute EtOH	52,53
W-7	1.28	1.73	As in W-4	As in W-4	3 times by decantations only; followed by washings with 95% EtOH and absolute EtOH as in W-6.	52,53

[a]50% Ni–50% Al alloy was always used.
[b]80% purity.

Taira and Kuroda have shown that the addition of bayerite accelerates the reaction of Raney alloy with water and, by developing the alloy with addition of bayerite, prepared an active Raney Ni that was supported on bayerite and resistant to deactivation.[57] The presence of bayerite probably promotes the crystallization of initially

formed alkali-soluble aluminum hydroxide into alkali-insoluble bayerite and hence favors an equilibrium of the reversible reaction shown in eq. 1.3 for the direction to give bayerite and sodium hydroxide. Thus, in the presence of bayerite, Raney alloy may be developed extensively with only a catalytic amount of sodium hydroxide. In the course of a study on this procedure, it has been found that, by using a properly prepared bayerite and suitable reaction conditions, an active Raney Ni that is not combined with the bayerite formed during the development can be prepared.[58] Under such conditions the alloy can be developed to such a degree as to produce the catalyst of the maximum activity at a low temperature with use of only a small amount of sodium hydroxide. The bayerite initially added as well as that newly formed can be readily separated from the catalyst simply by decantations. The bayerite thus recovered becomes reusable by treatment with a dilute hydrochloric acid. This procedure for the development of Raney alloy is advantageous not only for the use of only a small amount of sodium hydroxide but also to facilitate control of the highly exothermic reaction of aluminum oxidation which takes place very violently in the reaction of the alloy with a concentrated sodium hydroxide solution. Thus, in this procedure, the development of the alloy can be readily controlled to a desired degree that can be monitored by the amount of evolved hydrogen and adjusted with the amount of sodium hydroxide added and the reaction time. With a 40% Ni–60% Al Raney alloy, the degree of aluminum oxidation to give the highest activity has been found to be slightly greater than 80% and the resulting catalyst, denoted N-4, to be more active than the T-4 catalyst prepared using the same alloy. This result suggests that the T-4 catalyst has been overdeveloped (89% aluminum oxidation) for obtaining the highest activity.

The bayerite-promoted leaching procedure has also been applied to the development of single-phase $NiAl_3$ (42% Ni) and Ni_2Al_3 (59% Ni) alloys as well as to Co_2Al_9 (33% Co) and Co_2Al_5 (47% Co) alloys[59] that have been prepared with a powder metallurgical method by heating the green compacts obtained from the mixtures of nickel or cobalt and aluminum powder corresponding to their alloy compositions.[60] By use of the single-phase alloys it is possible to more accurately determine the degree of aluminum oxidation that may afford the highest activity of the resulting catalysts, since commercial alloys are usually a mixture of several alloy phases.[61] Table 1.4 summarizes the conditions and degrees of leaching with these single-phase alloys as well as with commercial alloys.

From the results in Table 1.4 it is seen that $NiAl_3$ is leached much more readily than commercial 40% Ni–60% Al alloy. Commercial 50% Ni–50% Al alloy is much less reactive toward leaching than $NiAl_3$ and 40% Ni–60% Al alloys, probably due to a larger content of far less reactive Ni_2Al_3 phase in the 50% Ni–50% Al alloy. Co_2Al_9 is by far the most reactive of the alloys investigated. Use of only 0.0097 molar ratio of NaOH to Al leached the alloy to a high degree of 85%. Co_2Al_5 and commercial 50% Co–50% Al alloys are very similar in their reactivity for leaching, and both are much less reactive than Co_2Al_9. Thus, the order in the reactivity for leaching of the alloys may be given roughly as follows: Co_2Al_9 > $NiAl_3$ > 40% Ni–60% Al > Co_2Al_5 ≥ 50% Co–50% Al ≥ 50% Ni–50% Al > > Ni_2Al_3.

TABLE 1.4 Leaching Conditions and Degrees of Leaching for Various Raney Ni–Al and Co–Al Alloys[a,b]

Alloy	Temperature for Leaching (°C)	NaOH Added (mol/mol Al)	Reaction Time (min)	Al Oxidized[c] (%)
$NiAl_3$	40	0.014	30	70
	40	0.014	90	83
	40	0.028	90	85
	40	1.4	90	89
	50[d]	1.4	150	90
	70[d]	1.4	150	93
40% Ni–60% Al	40	0.28	90	82
	50[d]	1.4	150	89
50% Ni–50% Al	40	2.1	90	80
	50[d]	2.1	150	83
	70[d]	2.1	150	85
Ni_2Al_3	50	2.9	90	78
	70	2.9	90	81
	70[e]	2.8	90	82
Co_2Al_9	40	0.0057	30	69
	40	0.0097	40	80
	40	0.0097	60	85
	40	0.016	90	87
	50[d]	1.1	150	91
	60[d]	1.1	150	95
50% Co–50% Al	40	0.21	90	77
	40	2.1	90	81
	50[d]	2.1	150	92
Co_2Al_5	40	0.21	90	79

[a]Data of Nishimura, S.; Kawashima, M.; Inoue, S.; Takeoka, S.; Shimizu, M.; Takagi, Y. *Appl. Catal.* **1991**, *76*, 19. Reprinted with permission from Elsevier Science.
[b]Unless otherwise noted, a mixture of 0.2 g alloy and 0.4 g bayerite was stirred in 4 ml of distilled water at 40°C, followed by addition of 0.12 ml of 2% sodium hydroxide solution. After 30 min of stirring, an additional amount of sodium hydroxide solution was added, if necessary.
[c]The degree of leaching (% of Al oxidized of the Al in the alloy) was calculated from the amounts of the evolved hydrogen and the hydrogen contained in the catalyst, assuming that 1 mol of Al gives 1.5 mol of hydrogen. The amount of hydrogen contained in the catalyst was determined by the method described previously (see Nishimura et al., Ref. 58).
[d]The alloy was leached by the T-4 procedure.
[e]The alloy was leached by a modified W-7 procedure in which a sodium hydroxide solution was added to the alloy suspended in water.

Figures 1.1*a–c* show the relationships between the catalytic activity and the degree of development that have been studied in the hydrogenation of cyclohexanone, naphthalene, and benzene over single phase $NiAl_3$ and Co_2Al_9 alloys. The rates of hydrogenation peak at around 82–86% degrees of development with both the alloys, and tend to decrease markedly with further development, irrespective of the compounds hydrogenated. It is noted that the cobalt catalyst from Co_2Al_9 is

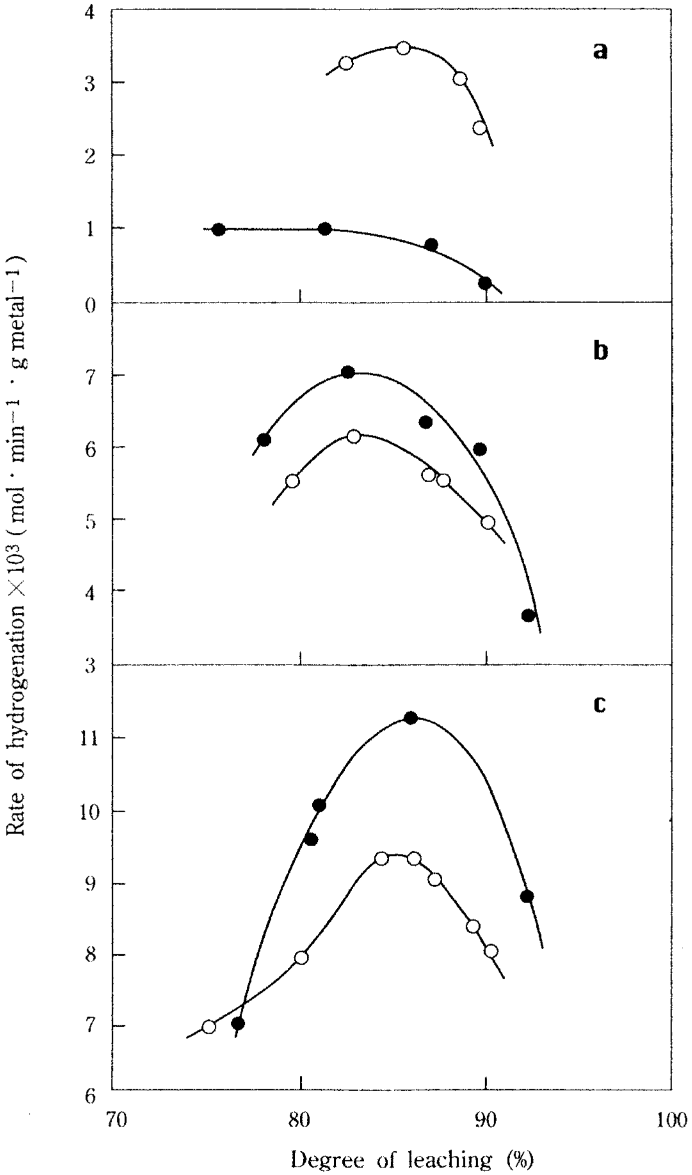

Figure 1.1 Variations in catalytic activity as a function of the degree of leaching with $NiAl_3$ (○) and Co_2Al_9 (●): (*a*) hydrogenation of cyclohexanone (1 ml) in *t*-BuOH (10 ml) at 40°C and atmospheric hydrogen pressure over 0.08 g of catalytic metal; (*b*) hydrogenation of naphthalene (3 g) to tetrahydronaphthalene in cyclohexane (10 ml) at 60°C and 8.5 ± 1.5 MPa H_2 over 0.08 g of catalytic metal; (*c*) hydrogenation of benzene (15 ml) in cyclohexane (5 ml) at 80°C and 7.5 ± 2.5 MPa H_2 over 0.08 g of catalytic metal. (From Nishimura, S.; Kawashima, M.; Inoue, S. Takeoka, S.; Shimizu, M.; Takagi, Y. *Appl. Catal.* **1991**, *76*, 26. Reproduced with permission of Elsevier Science.)

always more active than the nickel catalyst from $NiAl_3$ in the hydrogenation of both naphthalene and benzene. Since the surface area of the cobalt catalyst is considerably smaller than that of the nickel catalyst, the activity difference between the cobalt and nickel catalysts should be much greater on the basis of unit surface area. On the other hand, in the hydrogenation of cyclohexanone, the nickel catalyst is far more active than the cobalt catalyst, which appears to be related to a much greater amount of adsorbed hydrogen on the nickel catalysts than on the cobalt catalyst. Table 1.5 compares the activities of the nickel and cobalt catalysts obtained from various alloys in their optimal degrees of leaching. Ni_2Al_3 alloy was very unreactive toward alkali leaching, and the degree of development beyond 82% could not be obtained even with a concentrated sodium hydroxide solution at 70°C.

W-2 Raney Ni.[48] A solution of 380 g of sodium hydroxide in 1.5 liters of distilled water, contained in a 4-liter beaker, is cooled in an ice bath to 10°C, and 300 g of Ni–Al alloy powder (50% Ni) is added to the solution in small portions, with stirring, at such a rate that the temperature does not rise above 25°C. After all the alloy has been added (about 2 h is required), the contents are allowed to come to room temperature.

TABLE 1.5 Rates of Hydrogenation over Raney Catalysts from Various Ni–Al and Co–Al Alloys at Their Optimal Degrees of Leaching[a,b]

	Rate of Hydrogenation $\times 10^3$ (mol · min^{-1} · g metal^{-1})			
Starting Alloy	Cyclohexene[c]	Cyclohexanone[d]	Benzene[e]	Phenol[f]
$NiAl_3$	5.7 (87)	3.5 (86)	9.4 (86)	8.4 (88)
40% Ni–60% Al	5.2 (81)	2.6 (82)	9.3 (82)	5.2 (81)
50% Ni–50% Al	2.5 (82)	1.8 (85)	9.3 (83)	5.0 (83)
Ni_2Al_3	1.3 (80)	0.9 (81)	7.0 (82)	1.2 (80)
Co_2Al_9	1.3 (87)	1.0 (82)	11.3 (86)	5.5 (86)[g]
Co_2Al_5	—	0.39 (69)[g]	—	—
50% Co–50% Al	0.78 (69)	0.18 (77)	—	2.4 (77)[g]

[a]Data of Nishimura, S.; Kawashima, M.; Inoue, S.; Takeoka, S.; Shimizu, M.; Takagi, Y. *Appl. Catal.* **1991**, *76*, 19. Reprinted with permission from Elsevier Science.
[b]The catalysts were prepared before use each time and were well washed with distilled water by decantations, and then with *t*-BuOH. In the hydrogenations in cyclohexane, the *t*-BuOH was further replaced with cyclohexane. The rates of hydrogenation at atmospheric pressure were expressed by the average rates from 0 to 50% hydrogenation. The rates of hydrogenation at high pressures were expressed by the average rates during the initial 30 min. The figures in parentheses indicate the degrees of leaching.
[c]Cyclohexene (1 ml) was hydrogenated in 10 ml of *t*-BuOH at 25°C and atmospheric pressure with 0.08 g of catalytic metal.
[d]Cyclohexanone (1 ml) was hydrogenated in 10 ml of *t*-BuOH at 40°C and atmospheric pressure with 0.08 g of catalytic metal.
[e]Benzene (15 ml) was hydrogenated in 5 ml of cyclohexane at 80°C and 7.5 ± 2.5 MPa H_2 with 0.08 g of catalytic metal.
[f]Phenol (10 ml) was hydrogenated in 10 ml of *t*-BuOH at 80°C and 7.5 ± 2.5 MPa H_2 with 0.08 g of catalytic metal.
[g]Data from Inoue, S. Master's thesis, Tokyo Univ. Agric. Technol. (1990).

After the evolution of hydrogen slows down, the reaction mixture is allowed to stand on a steam bath until the evolution of hydrogen again becomes slow (about 8–12 h). During this time the volume of the solution is maintained by adding distilled water if necessary. The nickel is allowed to settle, and most of the liquid is decanted. Distilled water is then added to bring the solution to the original volume; the solution is stirred and then decanted. The nickel is then transferred to a 2-liter beaker with distilled water, and the water is again decanted. A solution of 50 g of sodium hydroxide in 500 ml of distilled water is added; the catalyst is suspended and allowed to settle; and the alkali is decanted. The nickel is washed by suspension in distilled water and decantation until the washings are neutral to litmus and is then washed 10 times more to remove the alkali completely (20–40 washings are required). The washing process is repeated 3 times with 200 ml of 95% ethanol and 3 times with absolute ethanol. The Raney nickel contained in the suspension weighs about 150 g.

W-6 (and also W-5 and W-7) Raney Ni.[52] A solution of 160 g of sodium hydroxide in 600 ml of distilled water, contained in a 2-liter Erlenmeyer flask, is allowed to cool to 50°C in an ice bath. Then 125 g of Raney Ni–Al alloy powder (50% Ni) is added in small portions during a period of 25–30 min. The temperature is maintained at 50 ± 2°C by controlling the rate of addition of the alloy and the addition of ice to the cooling bath. When all the alloy has been added, the suspension is digested at 50 ± 2°C for 50 min with gentle stirring. The catalyst is then washed with three 1-liter portions of distilled water by decantation. The catalyst is further washed continuously under about 0.15 MPa of hydrogen (an appropriate apparatus for this washing process is described in the literature cited). After about 15 liters of water has passed through the catalyst, the water is decanted from the settled sludge, which is then transferred to a 250-ml centrifuge bottle with 95% ethanol. The catalyst is washed 3 times by shaking, not stirring, with 150-ml portions of 95% ethanol; each addition is being followed by centrifuging. In the same manner the catalyst is washed 3 times with absolute ethanol. The volume of the settled catalyst in ethanol is about 75–80 ml containing about 62 g of nickel and 7–8 g of aluminum. The W-5 catalyst is obtained by the same procedure as for W-6 except that it is washed at atmospheric pressure without addition of hydrogen. The W-7 catalyst is obtained by the same developing procedure as for W-6, but the continuous washing process described above is eliminated. The catalyst so prepared contains alkali, but may be advantageous, such as for the hydrogenations of ketones, phenols, and nitriles.

T-4 Raney Ni.[55] To a mixture of 2 g of Raney Ni–Al alloy (40% Ni) and 10 ml water in a 30-ml Erlenmeyer flask immersed in a water bath of 50°C, 0.4 ml of 20% aqueous sodium hydroxide is added with vigorous stirring with caution to prevent the reaction from becoming too violent. In about 1 h the partly leached Raney alloy begins to react with water and turn gray in color, and the reaction almost subsides in about 1.5 h. Then 6 ml of 40% aqueous sodium hydroxide is added at one time with continued stirring. The digestion is continued for one additional hour with good stirring until the upper layer becomes white. The catalyst is washed by stirring and

decanting 4 times with each 15 ml of water of 50°C, and then 3 times with the same volume of ethanol at room temperature. A specimen of the catalyst thus prepared contained 13.3% of aluminum and a little aluminum hydroxide.

N-4 Raney Ni.[58] In a 10-ml conical flask are placed 0.5 g of Raney Ni–Al alloy powder (40% Ni) and 1 g of the bayerite prepared by the procedure described below. To this 10 ml of distilled water is added and stirred well at 40°C. Then 0.03 ml of 20% sodium hydroxide solution is added and the mixture stirred for 30 min at the same temperature, in which a violent reaction almost subsides. A further 0.3 ml of 20% sodium hydroxide solution is added and the mixture stirred for 1 h at 40°C. Then the upper layer is decanted carefully to avoid leakage of the catalyst. The catalyst is washed 3 times with each 10 ml of distilled water and 3 times with the same volume of methanol or ethanol. A specimen of the catalyst thus prepared contains 0.192 g of nickel, 0.050 g of aluminum, and 0.036 g of acid-insoluble materials. The bayerite suspensions are combined and acidified with a dilute hydrochloric acid, and then warmed to 50–60°C, when the gray color of the bayerite turns almost white. The bayerite is collected, washed well with water, and then dried in vacuo over silica gel. The bayerite thus recovered amounts to 1.4–1.6 g and can be reused for the preparation of a new catalyst.

The bayerite, which may promote the efficient development of a Raney alloy, can be prepared as follows: 20 g of aluminum grains is dissolved into a sodium hydroxide solution prepared from 44 g of sodium hydroxide and 100 ml of water. The solution is diluted to 200 ml with water and then CO_2 gas is bubbled into the solution at 40°C until small amounts of white precipitates are formed. The precipitates are filtered off and more CO_2 gas is bubbled into the filtrate. Then the solution is cooled gradually to room temperature under good stirring and left overnight with continued stirring. The precipitates thus produced (20–24 g) are collected, washed with warm water, and then dried in vacuo over silica gel. The bayerite thus prepared usually contains a small amount of gibbsite. The bayerite recovered from the catalyst preparation is less contaminated with gibbsite.

Leaching of $NiAl_3$ Alloy to a Desired Degree by the N-4 Procedure.[59] A mixture of 0.2 g of $NiAl_3$ alloy powder and 0.4 g of bayerite is placed in a 30-ml glass bottle connected to a gas burette and the mixture stirred with addition of 4 ml of distilled water at 40°C. Then 0.12 ml of 2% sodium hydroxide solution (NaOH/Al = 0.014 mol/mol) is added to the mixture. After stirring for 30 min, an additional amount of sodium hydroxide solution required for a desired degree of leaching (see Table 1.4) is added and further stirred until the amounts of evolved hydrogen and adsorbed hydrogen [~8–9 ml at standard temperature and pressure (STP)] indicate the desired degree. Then the catalyst is washed in the same way as in the preparation of N-4 catalyst.

Activation of Raney Ni by Other Metals. The promoting effect of various transition metals for Raney Ni has been the subject of a number of investigations and patents.[62] Promoted Raney nickel catalysts may be prepared by two methods: (1) a promoter metal is added during the preparation of the Ni–Al alloy, followed by

leaching activation of the resulting alloy; (2) Raney Ni is plated by some other metal with use of its salt after leaching activation or during leaching process. The latter method has often been used in the promotion with a noble metal such as platinum. Paul studied the promoted catalysts from Ni–Al alloys containing Mo, Co, and Cr.[63] Various promoted catalysts prepared from ternary as well as quaternary Raney alloys have been prepared by Russian groups.[64] The catalysts from Ni–Al–Cr (46–48:52–50:2), Ni–Al–Ti (3–4 wt% Ti) and Ni–Al–Cr–B (46:52:1.9:0.1) alloys showed higher activities and stabilities than unpromoted one. The catalyst from the Ni–Al–Cr–B alloy gave 70–77% yield of *p*-xylylenediamine in the hydrogenation of terephthalonitrile in dioxane or methanol with liq. ammonia at 100°C and 9 MPa H_2.[64a] The catalyst from the alloy containing 2.75% Ti had an activity 3 times that of the catalyst from the Ni–Al–Cr alloy and maintained its activity much longer in the hydrogenation of glucose at 120°C and 6 MPa H_2.[64c] Ishikawa studied a series of catalysts from ternary alloys containing Sn, Pb, Mn, Mo, Ag, Cr, Fe, Co, and Cu.[65] Promoting effects were always observed in the hydrogenation of nitrobenzene, cyclohexene, and phenol, when the metals were added in small amounts. In the hydrogenation of glucose, the metals could be classified into two groups: one that gave highest rates at rather large amounts (10–20 atom%) (Mn, Sn, Fe, Mo), and one that showed promoting effects when added only in small amounts (< 1 atom%) (Pb, Cu, Ag, Cr, Co). In the hydrogenation of acetone, marked promoting effects of Mo, Sn, and Cr were observed in the large amounts of 20, 15, and 10 atom%, respectively. Montgomery systematically studied the promoting effects of Co, Cr, Cu, Fe, and Mo with the Raney Ni catalysts prepared from ternary alloys: 58% Al–(42–x)% Ni–x% each promoter metal. The alloys were activated by the procedure for a W-6 catalyst, but digestion was extended to 4 h at 95°C, washing was by decantation, and the catalyst was stored under water. Aluminum was extracted from the alloy to the extent of 95 ± 2% with the exception of the Ni–Cr–Al alloys where it ranged from 91 to 92%. The Co, Cr, and Fe in the alloys were lost during the leaching process when the metal/Ni ratio was below 5/100, and the loss diminished as the ratio was increased. In the case of Ni–Al–Mo alloys no more than 40% of the original Mo remained in the resulting catalysts; about 32% were retained on the average. The activities of the promoted catalysts were compared in the hydrogenation of sodium itaconate, sodium *p*-nitrophenoxide, acetone, and butyronitrile at 25°C and atmospheric hydrogen pressure. In general, Mo was found to be the most effective promoter. Fe promoted more effectively than the other metals the hydrogenation of sodium *p*-nitrophenoxide. The catalyst containing 6.5% Fe was twice as active as the unpromoted catalyst. In the hydrogenation of acetone and butyronitrile, all the promoted catalysts tested were more active than the unpromoted catalyst with the exception of the 10% Cr-promoted catalyst. The most pronounced effect was found in the hydrogenation of butyronitrile with the 2.2% Mo-promoted catalyst where the rate was increased to 6.5 times that of the unpromoted catalyst. It has been found that the improved activity of the promoted Raney nickel catalysts are not due to a particle size effect. Results of the promoted catalysts with optimum activity in which at least a 20% increase in activity has been obtained are summarized in Table 1.6.

TABLE 1.6 Hydrogenation of Organic Compounds with Promoted Raney Nickel Catalysts with Optimum Activity[a]

Compound Hydrogenated	Promoter (M)	Composition M/(Ni + M + Al) × 100	$k_{promoted}/k_{unpromoted}$[b]	Increase in Activity (%)
Butyronitrile[c]	Mo	2.2	6.5	550
	Cr	1.5	3.8	280
	Fe	6.5	3.3	230
	Cu	4.0	2.9	190
	Co	6.0	2.0	100
Acetone[d]	Mo	2.2	2.9	190
	Cu	4.0	1.7	70
	Co	2.5	1.6	60
	Cr	1.5	1.5	50
	Fe	6.5	1.3	30
Na *p*-nitrophenoxide[e]	Fe	6.5	2.1	110
	Mo	1.5	1.7	70
	Cr	1.5	1.6	60
	Cu	4.0	1.3	30
Na itaconate[f]	Mo	2.2	1.2	20

[a]Data of Montgomery, S. R. in *Catalysis of Organic Reactions*; Moser, W. R., Ed.; Marcel Dekker: New York, 1981; p 383. Reprinted with permission from Marcel Dekker Inc.
[b]The rate of hydrogenation (mmol · min^{-1} · g^{-1}) at 25°C and atmospheric pressure.
[c]2 g in 100 ml of 5% H_2O–95% MeOH (0.1*M* solution in NaOH).
[d]50 g in 100 ml of 50% acetone–50% H_2O (0.1*M* solution in NaOH).
[e]2.3 g in 100 ml of 5% H_2O–95% MeOH (0.1*M* solution in NaOH).
[f]2.7 g in 100 ml of 20% H_2O–80% MeOH (0.1*M* solution in NaOH).

Delépine and Horeau[66] and Lieber and Smith[67] have found that the catalytic activity of Raney Ni is greatly enhanced by treatment with or by addition of small amounts of chloroplatinic acid. The platinized Raney Ni of Delépine and Horeau, simply prepared by treating Raney Ni with an alkaline chloroplatinic acid, was highly active for the hydrogenation of carbonyl compounds in the presence of a small amount of sodium hydroxide. Lieber and Smith activated Raney Ni by adding small amounts of chloroplatinic acid to a Raney Ni–acceptor ethanol mixture just prior to the introduction of hydrogen. The enhancing effect obtained was markedly beyond that which would be expected on the basis of the quantity of platinum involved. The Raney Ni activated by the method of Smith et al. was found to be more effective in the hydrogenation of nitro compounds than the one platinized by the method of Delépine and Horeau.[67,68] The largest promoting effect was obtained when the rates of hydrogenation with Raney Ni alone were small. For example, the rate of hydrogenation of ethyl *p*-nitrobenzoate (0.05 mol) in 150 ml 95% ethanol solution at room temperature and atmospheric pressure was increased from 3.9 ml H_2 uptake per 100 s with unpromoted catalyst (4.5 g) to 502 ml per 100 s with the catalyst promoted by the addition of 0.375 mmol of chloroplatinic acid (0.073 g Pt), compared to the corresponding rate increase from 115 to 261 ml in the case of nitrobenzene.[69] Nishimura platinized T-4 Raney Ni by adding an alkaline chloroplatinic acid solution during the leaching process of Ra-

ney alloy.[55] The resulting catalyst was found to be more active than that platinized by the method of Delépine and Horeau in the hydrogenation of ketones, quinoline, benzonitrile, and cyclohexanone oxime at 25°C and atmospheric hydrogen pressure (Table 1.7). Blance and Gibson prepared Raney Ni promoted by platinum from a Ni–Al alloy containing 2% of platinum in order to avoid the poisoning by chloride ion.[70] In hydrogenation of ketones in the presence of alkali, this catalyst was at least as effective as or even more effective than the catalyst platinized with a method improved by Blance and Gibson, by adding triethylamine (3.3 mmol), chloroplatinic acid (0.04 mmol) and finally 10*M* sodium hydroxide (1.2 mmol) to a rapidly stirred suspension of Raney Ni (0.5 g).

Voris and Spoerri were successful to hydrogenate 2,4,6-trinitro-*m*-xylene within a short time (45 min) in dioxane at 90°C and 0.3 MPa H_2 to give 2,4,5-triamino-*m*-xylene in a 99% yield,[71] and Décombe was successful to hydrogenate triphenylacetonitrile, diphenylacetonitrile, and α,α,α-butyldimethylacetophenone oxime to the corresponding primary amines quantitatively, using the platinized Raney Ni of Delépine and Horeau.[72]

Delépine and Horeau also compared the activating effects of the six platinum group metals on Raney Ni in the hydrogenation of carbonyl compounds. Osmium, iridium, and platinum were the most effective, ruthenium and rhodium followed them, and palladium was the least effective.[66]

Platinized T-4 Raney Ni.[55] To a suspension of 2 g of 40% Ni–Al alloy powder in 10 ml of water is added, with vigorous stirring in a water bath of 50°C, 0.05 g of chloroplatinic acid, $H_2PtCl_6 \cdot 6H_2O$, dissolved in 2 ml of water made alkaline with 0.4 ml of 20% aqueous sodium hydroxide. The procedure hereafter is exactly the same as

TABLE 1.7 Time (min) for Hydrogenation with T-4 Raney Ni and Platinized T-4 Raney Ni[a,b]

Compound Hydrogenated	g (mol)	H_2 Uptake (mol/mol)	Catalyst[c] T-4	T-4/Pt	T-4/Pt (Delépine–Horeau)
Cyclohexanone	3.93 (0.04)	1	17	10	13
Acetophenone	4.81 (0.04)	1	34	13	17
Quinoline	2.58 (0.02)	2	83	27	38
Benzonitrile	2.06 (0.02)	2	49	11	14
Cyclohexanone oxime	2.26 (0.02)	2	92	17	19

[a]Data of Nishimura, S. *Bull. Chem. Soc. Jpn.* **1959**, *32*, 61. Reprinted with permission from Chemical Society of Japan.
[b]The compound was hydrogenated in 20 ml of 95% EtOH at 25°C and atmospheric pressure.
[c]The catalyst was prepared from 2 g of 40% Ni–Al alloy by the procedure for the T-4 catalyst each time before use. T-4: unpromoted catalyst; T-4/Pt: the catalyst platinized during leaching process with 0.05 g of chloroplatinic acid (0.0185 g Pt); T-4/Pt (Delépine–Horeau): T-4 Raney Ni platinized with 0.05 g of chloroplatinic acid by the method of Delépine and Horeau (Ref. 66).

for the preparation of the T-4 catalyst described above. It is noted that an incomplete digestion, which is indicated by the gray color of the upper layer of the reaction mixture, does not develop the effective activation by the platinum.

1.1.4 Urushibara Nickel

Urushibara nickel catalysts[73] are prepared by activating the finely divided nickel deposited on zinc dust from an aqueous nickel salt, by either an alkali or an acid. A uniform deposition of finely divided nickel particles on zinc dust, which is obtained by the rapid addition of a concentrated aqueous solution of nickel chloride to a suspension of zinc dust in water at a temperature near 100°C with efficient stirring during the addition, leads to a catalyst of high activity with the subsequent activation by caustic alkali or an acid such as acetic acid.[15,16] The activation process by alkali or acid has been assumed to involve the dissolution of the basic zinc chloride, which has been produced on an active nickel surface during the reaction of zinc dust with nickel chloride in water, as presumed from the dissolution of a large quantity of chloride ion by treatment with caustic alkali and by comparison of the X-ray diffraction patterns of nickel–zinc powders before and after treatment.[74] This assumption was later shown to be totally valid by Jacob et al. by means of X-ray photoelectron spectroscopy (XPS), X-ray diffraction, scanning electron microscopy (SEM) combined with X-ray energy dispersion (EDX), and wet chemical analysis.[75] The Urushibara catalyst obtained by activation with a base is abbreviated as U-Ni-B and the catalyst obtained with an acid as U-Ni-A. It is noted that U-Ni–A contains a much smaller amount of zinc (~0.5 g/g Ni) than U-Ni-B (~5 g/g Ni) and is advantageous over U-Ni-B in those hydrogenations where the presence of alkali should be avoided. An interesting application of U-Ni-A is seen in the synthesis of *N*-arylnitrones by hydrogenation of an aromatic nitro compound in the presence of an aldehyde (see eq. 9.66).

Urushibara Ni B (U-Ni–B).[15] Zinc dust (10 g) and about 3 ml of distilled water are placed in a 100-ml round flask equipped with a stirrer reaching the bottom of the flask, and heated on a boiling water bath. To this mixture is added 10 ml of an aqueous hot solution of nickel chloride containing 4.04 g of nickel chloride, $NiCl_2{\cdot}6H_2O$, with vigorous stirring in a few seconds. The resulting solids are collected on a glass filter by suction, washed with a small quantity of distilled water, and then transferred into 160 ml of 10% aqueous sodium hydroxide solution, and digested at 50–60°C for 15–20 min with occasional stirring. The catalyst thus obtained is washed by decantation 2 times with each 40 ml of distilled water warmed to 50–60°C, and then with the solvent for hydrogenation, such as, ethanol.

Urushibara Ni A (U-Ni–A).[16] The solids prepared by the reaction of zinc dust with aqueous nickel chloride solution, in the same way as described above, are transferred into 160 ml of 13% acetic acid and digested at 40°C until the evolution of hydrogen gas subsides or the solution becomes pale green. The catalyst can be washed with water on a glass filter under gentle suction with care to prevent the catalyst from contacting air, and then with the solvent for hydrogenation.

1.1.5 Nickel Boride

Paul et al. prepared an active nickel catalyst by reducing nickel salts such as nickel chloride or nickel acetate with sodium or potassium borohydride.[17] The products thus obtained are neither magnetic nor pyrophoric and do not dissolve as quickly as Raney Ni in hydrochloric acid or potassium triiodide, and showed an activity comparable to or slightly inferior to Raney Ni, as examined in the hydrogenation of safrole, furfural, and benzonitrile at room temperature and atmospheric pressure. Usually, the catalyst from nickel acetate was slightly more active than that from nickel chloride. In the hydrogenation of safrole, the catalysts exhibited greater resistance to fatigue than Raney Ni in a series of 29 hydrogenations. The average composition of the catalysts deviated very little from a content of 7–8% boron and 84–85% nickel, which corresponded to the formula of Ni_2B. Hence, the catalysts have been denoted nickel borides. A more active catalyst was obtained by introduction of an alkali borohydride into the solution of the nickel salt, since the formation of nickel boride was always accompanied by decomposition of the alkali borohydride according to eq. 1.4. The overall reaction is formulated as in eq. 1.5, although the boron content of the products has been reported to vary with the ratio of reactants used in preparation.[76,77]

$$NaBH_4 + 2H_2O \rightarrow NaBO_2 + 4H_2 \tag{1.4}$$

$$2Ni(OAc)_2 + 4NaBH_4 + 9H_2O \rightarrow Ni_2B + 4NaOAc + 3B(OH)_3 + 12.5H_2 \tag{1.5}$$

Later, Brown and Brown found that the nickel boride prepared by reaction of nickel acetate with sodium borohydride in an aqueous medium is a granular black material and differs in activity and selectivity from a nearly colloidal catalyst prepared in ethanol.[18,19] The boride catalyst prepared in aqueous medium, designated P-1 Ni, was more active than commercial Raney Ni toward less reactive olefins, and exhibited a markedly lower tendency to isomerize olefins in the course of the hydrogenation. The boride catalyst prepared in ethanol, designated P-2 Ni, was highly sensitive to the structure of olefins, more selective for the hydrogenation of a diene or acetylene, and for the selective hydrogenation of an internal acetylene to the *cis* olefin (see eq. 3.13; also eqs. 4.24 and 4.25).[78,79] The high selectivity of the P-2 catalyst over the P-1 catalyst has been related to the surface layer of oxidized boron species, which is produced much more dominantly during the catalyst preparation in ethanol than in water.[80] The reaction of sodium borohydride with nickel salts containing small quantities of other metal salts provides a simple technique for the preparation of promoted boride catalysts. The Ni–Mo, Ni–Cr, Ni–W, and Ni–V catalysts thus prepared were distinctly more active than the catalyst without a promoter in the hydrogenation of safrole. The Ni–Cr catalyst was almost twice as active as Raney Ni in the hydrogenation of furfural.[17] The preparation of Ni boride catalyst in the presence of silica provides a supported boride catalyst with a highly active and stable activity.[81]

There appear to be known only few examples where Ni boride catalysts have been applied to the hydrogenation of the aromatic nucleus. Brown found no evidence for reduction of the aromatic ring. Benzene failed to reduce at all in 2 h at 25°C and atmospheric pressure, although pyrocatechol was readily reduced to cyclohexanediol over P-1 Ni in an autoclave.[77] Nishimura et al. studied the rates of hydrogenation of benzene, toluene, and *o*-xylene over Raney Ni and P-1 Ni as catalysts in methylcyclohexane (cyclohexane in the case of toluene) at 80°C (100°C for *o*-xylene) and the initial hydrogen pressure of 7.8 MPa.[82] It is seen from the results in Table 1.8 that P-1 Ni is as active as or only slightly inferior to Raney Ni in the activity on the basis of unit weight of metal, but it is far more active than Raney Ni when the rates are compared on the basis of unit surface area. It is noted that the order in hydrogen pressure for the rate of hydrogenation of benzene is greater for P-1 Ni (1.04) than for Raney Ni (0.58). These results may be related to the fact that the Raney Ni retains a large amount of adsorbed hydrogen while the P-1 Ni practically no hydrogen.

Nakano and Fujishige prepared a colloidal nickel boride catalyst by reducing nickel chloride with sodium borohydride in ethanol in the presence of poly(vinylpyrrolidone) as a protective colloid.[83] Catalytic activity of the colloidal catalyst was higher than P-2 Ni boride for the hydrogenation of acrylamide and markedly enhanced by the addition of sodium hydroxide in the hydrogenation of acetone.[84]

Ni Boride (by Paul et al.).[17] In this procedure, 27 ml of a 10% aqueous solution of sodium borohydride is added with stirring, for about 20 min, to 121 ml of a 5% aqueous solution of nickel chloride hexahydrate (equivalent to 1.5 g Ni). Hydrogen is liberated, while voluminous black precipitates appear; the temperature may rise to 40°C. When all the nickel has been precipitated, the supernatant liquid is colorless

TABLE 1.8 Rates of Hydrogenation of Benzene, Toluene, and *o*-Xylene over Raney Ni and P-1 Ni Catalysts[a,b]

	Rate of Hydrogenation × 10^3 (mol · min^{-1} · g $metal^{-1}$)		Rate of Hydrogenation × 10^5 [mol · min^{-1} · $(m^2)^{-1}$][c]	
Compound	Raney Ni[d]	P-1 Ni[e]	Raney Ni[d]	P-1 Ni[e]
Benzene	8.3	6.3	8.1	30.0
Toluene	3.3	2.7	3.2	12.9
o-Xylene	2.2	2.2	2.2	10.5

[a]Nishimura, S.; Kawashima, M.; Onuki, A. Unpublished results; Onuki, A. Master's thesis, Tokyo Univ. Agric. Technol. (1992).
[b]The compound (10 ml) was hydrogenated in 10 ml methylcyclohexane (cyclohexane for toluene) at 80°C (100°C for *o*-xylene) and the initial hydrogen pressure of 7.8 MPa over the catalyst containing 0.08 g of catalytic metal and prepared before use. The rates (at the initial stage) were obtained by an extrapolation method to get rid of an unstable hydrogen uptake at the initiation.
[c]The surface areas were measured by means of Shimazu Flow Sorb II.
[d]A $NiAl_3$ alloy was leached by the procedure for the N-4 catalyst to an 88% degree of development.
[e]The catalyst was prepared by reduction of nickel acetate with $NaBH_4$ in water according to the procedure of Brown, C. A. *J. Org. Chem.* **1970**, *35*, 1903.

and has a pH approaching 10. The black precipitates are filtered and washed thoroughly, without exposure of the product to air. The catalyst can be kept in stock in absolute ethanol.

P-1 Ni Boride.[18,77] Nickel acetate tetrahydrate (1.24 g, 5.0 mmol) in 50 ml distilled water is placed in a 125-ml Erlenmeyer flask connected to a mercury bubbler and flushed with nitrogen. To the magnetically stirred solution, 10 ml of a 1.0*M* solution of sodium borohydride in water is added over 30 s with a syringe. When gas evolution has ceased, a second portion of 5.0 ml of the borohydride solution is added. The aqueous phase is decanted from the granular black solid and the latter washed twice with 50 ml of ethanol, decanting the wash liquid each time.

P-2 Ni Boride.[19,78] Nickel acetate tetrahydrate (1.24 g, 5.0 mmol) is dissolved in approximately 40 ml of 95% ethanol in a 125-ml Erlenmeyer flask. This flask is attached to a hydrogenator, which is then flashed with nitrogen. With vigorous stirring, 5.0 ml of 1*M* sodium borohydride solution in ethanol is injected. When gas evolution from the mixture has ceased, the catalyst is ready for use.

P-2 Ni Boride on SiO_2.[81] Finely powdered nickel acetate tetrahydrate (186.6 mg, 0.75 mmol) is placed in a flask, flushed with nitrogen, and to this 9 ml of degassed ethanol is added to dissolve the nickel salt by shaking under nitrogen (solution I). To 500 mg of finely powdered sodium borohydride is added 12.5 ml of ethanol and 0.5 ml of 2*M* aqueous sodium hydroxide, the mixture shaken for 1 min, the solution filtered, and the clear filtrate is immediately degassed and stored under nitrogen (solution II). In a flask is placed 500 mg silica gel [Merck, Artide 7729; ϕ ~0.08 (phase) mm], degassed for 15 min in vacuo, and flushed with nitrogen. To this 6 ml of solution I is added under a stream of nitrogen, evacuated, and flushed with nitrogen, and then 1 ml of solution II is added and shaken for 90 min under nitrogen. The P-2 Ni on SiO_2 thus prepared contains 0.5 mmol of Ni (~5.5 wt% Ni). Unsaturated compounds are very rapidly hydrogenated with the P-2/SiO_2 catalyst without solvent at 70–85°C and 10 MPa H_2. A turnover number of 89,300 [mmol product · (mmol catalyst)$^{-1}$] with an average catalyst activity of 124 [mmol product · (mmol catalyst)$^{-1}$ · min^{-1}] was obtained in the hydrogenation of allyl alcohol (1025 mmol) over 0.01 mmol catalyst at 95°C and 1 MPa H_2.

Colloidal Ni Boride.[83] Nickel(II) chloride ($NiCl_2 \cdot 6H_2O$, 0.020 mmol) and poly(vinylpyrrolidone) (2.0 mg) is dissolved in ethanol (18 ml) under hydrogen. To the solution, a solution of $NaBH_4$ (0.040 mmol) in ethanol (1 ml) is added drop by drop with stirring. A clear dark brown solution containing colloidal particles of nickel boride results. Stirring is continued further for 15 min to complete the hydrolysis of $NaBH_4$, which is accompanied by evolution of hydrogen. The colloidal nickel boride thus prepared is stable under hydrogen for more than several months, but decomposed immediately on exposure to air.

Besides Urushibara Ni and Ni boride catalysts, various finely divided nickel particles have been prepared by reaction of nickel salts with other reducing agents, such as sodium phosphinate;[20,85] alkali metal/liquid NH_3;[21] NaH-*t*-AmOH (designated Nic);[22,86]Na, Mg, and Zn in THF or Mg in EtOH;[24] or C_8K(potassium graphite)/THF–HMPTA (designated Ni–Gr1).[23,87] Some of these have been reported to compare with Raney Ni or Ni borides in their activity and/or selectivity.

1.2 COBALT CATALYSTS

In general, cobalt catalysts have been used not so widely as nickel catalysts in the usual hydrogenations, but their effectiveness over nickel catalysts has often been recognized in the hydrogenation of aromatic amines (Section 11.5) and nitriles (eqs. 7.24–7.30) to the corresponding primary amines, and also in Fischer–Tropsch synthesis.[88] The catalytic activity of reduced cobalt[89,90] and a properly prepared Raney Co[59] is even higher than those of the corresponding nickel catalysts in the hydrogenation of benzene (see Fig. 1.1*c*). The methods of preparation for cobalt catalysts are very similar to those used for the preparation of nickel catalysts.

1.2.1 Reduced Cobalt

The temperature required for the reduction of cobalt oxides to the metal appears to be somewhat higher than for the reduction of nickel oxide. The catalyst with a higher catalytic activity is obtained by reduction of cobalt hydroxide (or basic carbonate) than by reduction of the cobalt oxide obtained by calcination of cobalt nitrate, as compared in the decomposition of formic acid.[91] Winans obtained good results by using a technical cobalt oxide activated by freshly calcined powdered calcium oxide in the hydrogenation of aniline at 280°C and an initial hydrogen pressure of 10 MPa (Section 11.5).[92] Barkdoll et al. were successful to hydrogenate bis(4-aminophenyl)methane (100 parts) with use of a cobaltic oxide (10 parts) promoted by calcium hydroxide (15 parts) and sodium carbonate (6.5 parts) at 215°C and 12–22 MPa H_2.[93] Volf and Pasek obtained a high selectivity to primary amine with a cobalt catalyst modified by manganese (5%)[94] in the hydrogenation of stearonitrile at 150°C and 6 MPa H_2.[95]

Co–Kieselguhr.[96] To a mixture of 150 g of $Co(NO_3)_2 \cdot 6H_2O$ and 47 g of kieselguhr in 310 ml of water is added a solution of 124 g of $NaHCO_3$ dissolved in 2.5 liters of water with stirring. After warming the mixture at 80°C for 2 h, the solid is filtered, washed with water, and then dried. The basic carbonate of cobalt on kieselguhr thus prepared is reduced with hydrogen at 475°C for 2–3 h.

Co–Mn (5.2% Mn) (by Adam and Haarer).[94] A solution of 4480 g of $Co(NO_3)_2 \cdot 6H_2O$, 261 g of $Mn(NO_3)_2 \cdot 6H_2O$, and 47 g of 85% H_3PO_4 in 10 liters of H_2O is added slowly to a solution of 1900 g of Na_2CO_3 in 10 liters of H_2O, filtered, calcined at 300°C, molded, and calcined at 450°C. The catalyst is reduced with hydrogen at

290°C before use. The catalyst was used for the hydrogenation of adiponitrile and stearonitrile to the corresponding primary amines in high yields.[94,95]

1.2.2 Raney Cobalt

Compared to a large body of studies on Raney Ni catalysts, those on Raney Co appear to be rather few, perhaps because the lower activity in general and higher cost of Raney Co have found limited laboratory uses as well as industrial applications. In early studies, the preparation and use of Raney Co catalysts were described by Faucounau,[97] Dupont and Piganiol,[98] and Signaigo.[99] Faucounau prepared the catalyst by treating a 47% Co–Al alloy with an excess of 30% sodium hydroxide below 60°C until no more hydrogen was evolved (~12 h). The resulting catalyst was used at 100°C and 10 MPa H_2 for hydrogenation of olefinic compounds, aldehydes, ketones, and aromatic side-chain linkages; at 200°C the benzene nucleus could be reduced. Dupont and Piganiol obtained a catalyst of improved activity for the hydrogenation of limonene and alloocimene, but the activity was still only about $\frac{1}{400}$th of that of Raney Ni as compared in the hydrogenation of alloocimene under ordinary conditions. Signaigo developed a 50% Co–50% Al alloy by adding a concentrated sodium hydroxide solution to a suspension of the alloy in water under boiling conditions, and employed the catalyst for the hydrogenation of dinitriles to diamines in high yield at 10–13 MPa H_2. Use of nickel catalysts led to larger amounts of condensed amine products. A detailed study by Aller on a 46% Co and 48–50% Al alloy has shown that, in contrast to Raney Ni, it is necessary to use fine-mesh alloy powders (200–300 mesh) to obtain a Raney Co of high activity. The use of the coaster alloy powders tended to give massive, agglomerated catalysts that did not disperse effectively, resulting in poor activity. Further, it has been clearly shown that treatment of the Raney Co alloys with alkali at higher temperatures (> 60°C) results in the catalysts of decreased activity with the low aluminum contents (< 4%). Treatment at 100°C resulted in almost complete removal of aluminum from the cobalt catalyst (0.07% remaining), compared to 8.8% residual aluminum in the corresponding Raney Ni. By careful selection of the alloy particle size and developing temperature (15–20°C), Aller obtained Raney Co catalysts that exhibited high activity for the hydrogenation of mesityl oxide under mild conditions.[100] The catalyst contained 7.1% of Al and had a surface area of 15.8 $m^2 \cdot g^{-1}$,[101] as determined by the fatty acid adsorption technique of Smith and Fuzek.[102] It is noted that the surface area is much smaller than those reported by Smith and Fuzek for Raney Ni catalysts (49–50 $m^2 \cdot g^{-1}$). Examples that show the high activity and/or selectivity of Raney Co catalysts for the hydrogenation of nitriles to primary amines are seen in eqs. 7.24–7.26. Taira and Kuroda prepared Raney Co–Mn–Al_2O_3 catalyst by developing Raney Co–Mn–Al (40 : 5 : 55) alloy suspended in water in the presence of bayerite and a small amount of alkali.[57] The catalyst was highly active and durable for repeated use in the hydrogenation of adiponitrile in the presence of ammonia, affording a 96.2% yield of 1,6-hexanediamine (see eq. 7.26). As in the preparation of N-4 Raney Ni, the Raney Co–Al alloys can be leached to the desired extents without difficulty by developing in the presence of bayerite and a small amount of alkali. This method is especially effective for the development of the highly reactive Co_2Al_9 alloy (32.6%

Co) to obtain the catalyst of high activity.[59] Catalysts with the greatest activity have been obtained by developing the alloy to the degree of 82–85% with use of only 0.0097 molar ratio of NaOH to the Al in the alloy (see Table 1.4 and Fig. 1.1), while the surface area became largest around 80% degree of development. The Raney Co catalyst thus obtained was more active than the Raney Ni similarly obtained from $NiAl_3$ alloy in the hydrogenation of naphthalene to tetrahydronaphthalene at 60°C and 8.5 MPa H_2 and of benzene to cyclohexane at 80°C and 7.5 MPa H_2 in cyclohexane, while the Raney Ni was several times more active than the Raney Co in the hydrogenation of cyclohexanone in *t*-butyl alcohol at 40°C and atmospheric hydrogen pressure (see Fig. 1.1).

Raney Co (by Aller).[100] In this procedure 200 g of 200–300-mesh Raney Co alloy (46% Co) is added in small portions to a solution of 240 g of sodium hydroxide in 960 ml of distilled water; 50 ml of ethanol is added to reduce frothing. Good stirring is maintained throughout the addition, with the temperature held at 15–20°C by means of an immersed glass cooling coil. When the alloy addition is complete (1 h), stirring and cooling is continued for a further 2 h, and the mixture set aside overnight. The alkali is decanted off, the catalyst being washed 10 times by decantation with 1-liter portions of water, and finally with three 200-ml portions of ethanol.

Raney Co from Co_2Al_9 Alloy.[59] A mixture of 0.25 g of Co_2Al_9 alloy powder (through 325 mesh) and 0.5 g of bayerite in 4 ml of distilled water is stirred at 40°C with addition of 0.12 ml of 2% sodium hydroxide solution for about 1 h, when the catalyst leached to a degree of about 85% is obtained. The degree of development, which may be monitored by the amounts of evolved hydrogen and adsorbed hydrogen, can be adjusted by the reaction time. The upper layer is decanted and the catalyst washed 4 times with each 10 ml of distilled water, and then 4 times with the same volume of the solvent for hydrogenation, such as *t*-butyl alcohol. For the hydrogenation in cyclohexane, the *t*-butyl alcohol is further replaced with cyclohexane.

1.2.3 Cobalt Boride

Cobalt boride catalysts have been shown to be highly active and selective in the hydrogenation of nitriles to primary amines.[103,104] Barnett used Co boride (5%) supported on carbon for the hydrogenation of aliphatic nitriles and obtained highest yields of primary amines among the transition metals and metal borides investigated including Raney Co.[104] An example with propionitrile, where a 99% yield of propylamine was obtained in the presence of ammonia, is seen in eq. 7.29.

5% Co Boride–C.[104] Charcoal (20 g) in distilled water (8 ml) is soaked for 15 min. Cobalt nitrate (4.2 g) in water (20 ml) is added and the mixture heated gently to dryness. The charcoal is cooled in ice water and sodium borohydride (25 ml of 20% solution) is added slowly to avoid rapid effervescence. The mixture is allowed to stand for 16 h and is filtered, and the catalyst is washed with copious amounts of water, then

dried and stored under hydrogen. Although not pyrophoric, the catalyst is deactivated on standing in air.

1.2.4 Urushibara Cobalt

Urushibara Co catalysts can be prepared exactly in the same way as the corresponding Ni catalysts, using cobalt chloride hexahydrate instead of nickel chloride hexahydrate as starting material. Similarly as with Raney catalysts, Urushibara Co has been found to be more effective and selective than Urushibara Ni in the hydrogenation of nitriles, affording high yields of primary amines.[105,106]

1.3 COPPER CATALYSTS

Unsupported reduced copper is usually not active as a hydrogenation catalyst and tends to lose its activity at high temperatures. Sabatier prepared an active unsupported copper catalyst by slow reduction of black "tetracupric hydrate" with hydrogen at 200°C.[107] Sabatier and Senderens originally claimed that benzene could not be hydrogenated over copper catalyst,[108] while Pease and Purdum were successful in transforming benzene into cyclohexane at 140°C over an active copper catalyst obtained by slow reduction of the oxide in hydrogen at an initial temperature of 150°C (finally heated to 300°C).[109] According to Ipatieff et al., the hydrogenating activity of reduced copper is very dependent on the presence of traces of impurities, especially of nickel.[110] Pure copper catalyst prepared from precipitated hydroxide or basic carbonate and containing not less than 0.2% of oxygen catalyzed the hydrogenation of benzene with difficulty at 225°C and ordinary pressure, but it readily hydrogenated benzene at 350°C and a hydrogen pressure of 15 MPa. In contrast, the copper catalyst containing 0.1% of nickel oxide readily hydrogenated benzene at 225°C under normal pressure.[110] Thus copper catalysts are almost completely inactive toward the hydrogenation of benzene under usual conditions.[89,90] However, copper catalysts are known to be highly selective, as in partial hydrogenation of polynuclear aromatic compounds such as anthracene and phenanthrene (eqs. 11.79 and 11.80), and also in the selective hydrogenation of nitrobenzene to aniline without affecting the benzene nucleus.[111–113] Industrially it is an important component in the catalysts for methanol synthesis in lowering the operation temperature and pressure.[114] Adkins and co-workers have developed an efficient copper catalyst for the liquid-phase hydrogenation by combining copper and chromium oxides, known as *copper chromite* or *copper–chromium oxide*.[115,116] The catalyst was prepared by decomposing basic copper ammonium chromate and has been found to be effective in the hydrogenation of various organic compounds at high temperatures and pressures.[117] The instability in activity of the catalyst, owing to reduction to a red inactive compound, experienced in the hydrogenation of certain compounds (e.g., ethyl phenylacetate to pheneylethyl alcohol) has later been improved by incorporating barium, calcium, or magnesium oxide into the catalyst.[118,119] The catalyst has been shown to be particularly effective for the hydrogenation of carboxylic esters to alcohols[116,120] (Section 10.2). Relatively low activity

of copper catalysts for carbon–carbon double bonds over carbonyl functions has been applied to selective hydrogenation of unsaturated aldehydes to unsaturated alcohols (Section 5.2). Raney type Cu catalysts in combination with Zn, Cd, or Ag have been found to be selective for the hydrogenation of an α,β-unsaturated aldehyde to the corresponding unsaturated alcohol.

Reduced Cu (by Ipatieff et al.).[110] Copper nitrate (2 mol) is dissolved in 4 liters of distilled water, and the filtered solution is placed in an ~23-liter earthenware crock, together with an additional 8 liters of warm water. To this solution is added, with stirring, a warm, filtered solution of 2 mol of ammonium carbonate in 4 liters of water. After standing for 1 h, the mixture is filtered with suction. The filtered cake is washed on a Buchner funnel with 500 ml of water and then returned to the crock, where it is stirred with 16 liters of warm water for 15 min. After standing for 1 h the solution is filtered. The precipitate is dried at 180–190°C for 36 h in a porcelain dish covered with a watch glass. The copper oxide is prepared by heating the dry powder in a stream of nitrogen for 20 h at 400°C, and is reduced in a stream of hydrogen for 20 h at 225°C or 90 h at 100°C, whereby 99.3–99.8% reduction is obtained. Prolonged heating in hydrogen for 120 h at 200 and 225°C had a little detrimental effect on activity, whereas continued heating in hydrogen at 300 and 350°C lowered the activity decidedly, and at 400°C the catalyst was rapidly deactivated almost as much by 20 h as by 120 h.

Cu–Ba–Cr Oxide.[121] 900 ml of a solution (80°C) containing 260 g of hydrated copper nitrate, $Cu(NO_3)_2 \cdot 3H_2O$, and 31 g of barium nitrate is added to 720 ml of a solution (at 25°C) containing 151 g of ammonium dichromate and 225 ml of 28% ammonium hydroxide. The precipitate is filtered, and the cake is pressed with a spatula and sucked as dry as possible. The product is dried in an oven at 75–80°C for 12 h and then pulverized. It is decomposed in three portions in a casserole over a free flame. In carrying out the decomposition, the powder is continuously stirred with a spatula and the heating regulated so that the evolution of gases does not become violent. This is accomplished by heating only one side of the casserole and stirring the powder more rapidly when the decomposition has started to spread throughout the mass. During this process, the color of the powder changes from orange to brown and finally to black. When the entire mass has become black, the evolution of gases ceases, and the powder is removed from the hot casserole and allowed to cool. The combined product is then leached for 30 min with 600 ml of 10% acetic acid solution, filtered, and washed with 600 ml of water in 6 portions, dried for 12 h at 125°C, and pulverized. The product weighs 170 g.

The intermediate precipitate obtained by the reaction of copper nitrate with ammonium dichromate and ammonia has been shown to be $Cu(OH)NH_4CrO_4$,[122] and the decomposition of the precipitate to give the catalyst to be formulated as in eq. 1.6, by an X-ray diffraction study by Stroupe, although the catalysts obtained by decomposition at sufficiently controlled low temperature (350°C) are amorphous.[123] Catalysts previously used in liquid-phase hydrogenation below 300°C often show crystalline cupric chromite to have been largely reduced to the cuprous chromite

together with the reduction of cupric oxide to metallic copper, which can be converted to the oxidized form by burning off in air, as shown in eq. 1.6.

$$\begin{array}{ccc} 2Cu(OH)NH_4CrO_4 & \longrightarrow & CuO\text{–}CuCr_2O_4 + N_2 + 5H_2O \\ & & [H] \downarrow\uparrow [O] \\ & & Cu + Cu_2Cr_2O_4 \end{array} \qquad (1.6)$$

Raney Cu.[124] Faucounau prepared an active Raney copper catalyst by dissolving a fine powder of Dewarda's alloy (50% Al, 45% Cu, 5% Zn) slowly with a 30% sodium hydroxide solution precooled. When the attack by alkali has been completed (~12 h), the solution is warmed gently until the evolution of hydrogen gas ceases. After standing, the alkali solution is decanted and replaced by a fresh solution, this treating process being repeated twice, and then the solution is carried to boiling for a few minutes. The catalyst thus obtained is washed by decantation with water until the washings become neutral, and then washed with alcohol and stored under alcohol. Over the Raney Cu, aldehydes were hydrogenated to the alcohols at 125–150°C, ketones to alcohols at 95–125°C, allyl alcohol to propyl alcohol at 100°C, and limonene to carvomenthene at 200°C, under the initial hydrogen pressure of 10 MPa.[124] Wainwright has reviewed the preparation and utilization of Raney Cu and Raney Cu–Zn catalysts.[125]

1.4 IRON CATALYSTS

Iron catalysts have found only limited use in usual hydrogenations, although they play industrially important roles in the ammonia synthesis and Fischer–Tropsch process. Iron catalysts have been reported to be selective for the hydrogenation of alkynes to alkenes at elevated temperatures and pressures. Examples of the use of Raney Fe, Fe from $Fe(CO)_5$, and Urushibara Fe are seen in eqs. 4.27, 4.28, and 4.29, respectively.

Raney Fe.[126,127] In this procedure 150 g of 20% Fe–Al alloy powder is added in small portions to a solution of sodium hydroxide (250 g per 1000 ml). The reaction is very vigorous, and 3 h is necessary for the addition. At the end, the temperature is held at 80–90°C until evolution of hydrogen ceases. The treatment with alkali is then repeated, after which the iron is washed repeatedly with boiling water by decantation. It is fully washed free of alkali with absolute alcohol and stored under alcohol.

Urushibara Fe.[128] To a well-mixed zinc dust (25 g) and water (8 g) placed in a 50-ml beaker is added 9.68 g (2 g of Fe) of ferric chloride hexahydrate ($FeCl_3 \cdot 6H_2O$). The mixture is then well stirred with a glass rod. Soon a vigorous exothermic reaction starts, but subsides within about 10 s. To complete the reaction, the mixture is stirred until the color of the ferric ion disappears. The reaction mixture is washed with 400

ml of cold water, and then the washing is removed by filtration or decantation. The precipitated iron is then digested in 330 g of 15% acetic acid with occasional stirring at 60–70°C for about 20–25 min. At the end of the digestion, evolution of hydrogen gas subsides and the solid with adsorbed hydrogen comes up to the surface of the almost colorless solution. The solid is quickly collected on a glass filter, washed with 300 ml of cold water, and then washed with 100 ml of ethanol.

1.5 PLATINUM GROUP METAL CATALYSTS

The platinum group metals—ruthenium, rhodium, palladium, osmium, iridium and platinum—have all been used as hydrogenation catalysts. Platinum appears to be the first transition metal that was used as a catalyst for hydrogenation. In as early as 1863, Debus found that methylamine was produced by passing hydrogen cyanide vapor, mixed with hydrogen, over a platinum black.[129] Among the platinum metals, platinum and palladium have been by far the most widely used catalysts since the earliest stages of the history of catalytic hydrogenation. A characteristic feature of these metals is that they are active under very mild conditions, compared to the base metals, and have been conveniently used in the liquid-phase hydrogenation at room temperature and atmospheric or only slightly elevated pressure of hydrogen. Willstätter and Hatt found that benzene was hydrogenated to cyclohexane over a platinum black at room temperature and atmospheric pressure in acetic acid or without solvent.[130] Since then a number of aromatic nuclear hydrogenations have been made using platinum catalysts at room temperature and low hydrogen pressure. On the other hand, since early the twentieth century palladium catalysts have been widely employed for the selective hydrogenation of acetylenic and olefinic compounds under mild conditions. Ruthenium and rhodium had found little attention until the mid-1950s, but since then they have been widely used as highly active and selective catalysts for the hydrogenation of various compounds, in particular, for aromatic nucear hydrogenations. Osmium and iridium have found much less use than the four metals mentioned above, although high selectivity has often been recognized with these catalysts in some hydrogenations.

It has been recognized that the second-row group VIII metals (Ru, Rh, Pd) often show behavior different from that of the third-row group VIII metals (Os, Ir, Pt) in catalytic hydrogenation.[131] For example, the second-row metals all give substantial isomerization in olefin hydrogenation whereas the third-row metals give only little (Section 3.2). These characteristics have also been related to their difference in selectivity in various hydrogenations, such as in the selective hydrogenation of acetylenes and diolefins (Chapter 4 and Section 3.6), in the stereochemistry of hydrogenation of alicyclic and aromatic compounds (Sections 3.7 and 11.1.3), in the formation of intermediates in hydrogenation of aromatic compounds (e.g., see Section 11.2), and in the tendency for hydrogenolysis in the hydrogenation of vinylic and arylic ethers (Section 11.2.3 and 13.1.5). It is to be noted that palladium often shows a particularly high selectivity among the six platinum metals in these and other hydrogenations.

Platinum metal catalysts have been employed either in the form of unsupported fine particles of metal, usually referred to as blacks, or in the state supported on an inert

porous or nonporous material. Unsupported catalysts may also be prepared in a colloidal form by liberating metal in the presence of a suitable protective colloid. Unsupported catalysts still find wide use in laboratory hydrogenations and are preferred particularly in small-scale hydrogenation where loss of product should be avoided. On the other hand, supported catalysts have many advantages over unsupported catalysts. Supports permit greater efficiency in the use of an expensive metal by giving a larger exposed active surface and in some cases may facilitate metal recovery. Further, supported catalysts usually have a greater resistance to poisoning and are more stable at elevated temperatures and/or pressures. The activity and/or selectivity of a supported catalyst, however, may depend greatly on the physical and chemical nature of the support used. Most of the platinum metal catalysts supported on carbon or alumina are commercially available.

Synergistic effects in catalytic activity and/or selectivity have often been observed in cofused or coprecipitated mixed platinum metal catalysts. Binary oxide catalysts of rhodium, ruthenium, and iridium containing platinum, prepared by sodium nitrate fusion of a mixture of the two component salts, are reduced with hydrogen much more readily than the pure oxide of each metal. The resulting catalysts often show superior catalytic properties not possessed by either component alone. Optimum metal ratios may vary with the metals present and with the substrate to be hydrogenated. Marked synergism has been reported with the mixed oxides of rhodium–platinum,[132] ruthenium–platinum,[133] and iridium–platinum.[134] Similar synergism has also been observed with carbon-supported catalysts of rhodium–platinum,[135] palladium–platinum,[136] palladium–ruthenium,[137] and platinum–ruthenium[137] systems.

1.5.1 Platinum

1.5.1.1 Platinum Blacks. The method of Loew for preparing platinum black by adding a sodium hydroxide solution to a mixture of platinic chloride and formaldehyde in a cold aqueous solution[138] has been improved by Willstätter and Waldschmidt-Leitz[139] and Feulgen.[140] The original procedure has been modified to avoid passing into colloidal solution during the process of washing. Willstätter and Waldschmidt-Leitz employed a potassium hydroxide solution instead of aqueous sodium hydroxide. After the addition of alkali the temperature was raised to 55–60°C to secure the precipitation to yield coarse particles. Feulgen rendered the suspension of the catalyst in water acidic with acetic acid to prevent the particles from becoming colloidal during the subsequent washing process.

Voorhees and Adams[141] obtained an active platinum black from the platinum oxide prepared by fusing a mixture of chloroplatinic acid and sodium nitrate at 500–550°C. The platinum oxide is readily reduced to an active black with hydrogen in a solvent in the presence or absence of substrate. The platinum oxide–platinum black thus prepared has been shown to be very active in the hydrogenation of various organic compounds and is now widely used as Adams platinum oxide catalyst. Frampton et al. obtained a platinum oxide catalyst of reproducible activity by adding a dry powder of a mixture of 1 g of chloroplatinic acid and 9 g of sodium nitrate in its entirety to 100

g of molten sodium nitrate heated at 520°C.[142] It was noted that decreased activities were obtained with temperatures in excess of 540°C. Vandenheuvel prepared an active and stable platinum oxide catalyst by adding a mixture of chloroplatinic acid (7 g) and silicic acid (200 mesh, 20 g) to 70 g of molten sodium nitrate at 350°C.[143]

The reaction involved in the preparation of Adams platinum oxide may be expressed as follows:

$$H_2PtCl_6 + 6NaNO_3 \rightarrow Pt(NO_3)_4 + 6NaCl + 2HNO_3$$

$$Pt(NO_3)_4 \rightarrow PtO_2 + 4NO_2 + O_2 \qquad (1.7)$$

$$PtO_2 + H_2O \rightarrow PtO_2 \cdot H_2O$$

Keenan et al. have shown that the Adams platinum oxides prepared by the standard and modified procedures as well as those of commercial preparation contained alkaline sodium salts (1.1–2.0% as sodium), the presence of which strongly prevented the hydrogenation of benzene. However, when the oxide was reduced with hydrogen in methanol or in an acid medium and then washed, the sodium was largely removed and the resulting catalyst could hydrogenate benzene without addition of acetic acid.[144] The alkaline materials remaining in the catalyst may also have a profound effect in other hydrogenations (see, e.g., Sections 3.4 and 5.3.1). According to Cahen and Ibers, Adams platinum oxide is a mixture of Pt, α-PtO_2, and $Na_xPt_3O_4$ (platinum bronze); the α-PtO_2 is readily reduced to active metal with hydrogen but the $Na_xPt_3O_4$ is reduced only partly, although it shows catalytic activity.[145]

Brown and Brown prepared an active platinum catalyst by in situ reducing chloroplatinic acid (1 ml of 0.2*M* solution) in 40 ml ethanol by injecting 5.0 ml of 1*M* sodium borohydride in ethanol; the excess borohydride is destroyed by injecting 4.0 ml of 6*M* hydrochloric acid. The platinum catalyst thus prepared was nearly twice as active as a commercial Adams catalyst in the hydrogenation of 1-octene at 25°C and atmospheric hydrogen pressure.[146]

A platinum black almost free from alkaline or acidic impurities has been obtained by reducing platinum(II) hydroxide with hydrogen in water at room temperature and atmospheric pressure followed by washing with water. The reduction and washing process is repeated several times until the washing becomes neutral. The platinum(II) hydroxide was prepared by adding a lithium hydroxide solution to a suspension of platinum(II) chloride in hot water (90–95°C) with efficient stirring until the pH of the solution approximates 7.5–7.8 and the pH no longer changes on further standing. The platinum black thus prepared showed a characteristic behavior very similar to the platinum obtained from its vapor for the acetal formation and hydrogenation of 4-methylcyclohexanone in ethanol.[147]

Platinum Black (by Feulgen).[140] A solution of chloroplatinic acid (5 g) in water (5 ml) is mixed with formaldehyde solution (40%, 7 ml), and sodium hydroxide (5 g) dissolved in water (10 ml) is gradually added under cooling. The mixture is allowed

to remain for 30 min at ordinary temperature, then heated for 15 min at 55°C and poured into a 0.5-liter flask half-full of water.The flask is agitated violently for a few minutes, which causes the precipitate to settle in coarse particles, leaving an almost colorless supernatant liquid. The liquid is decanted, the flask is filled with water, and the water is strongly acidified with acetic acid. After violent agitation, the precipitate can be washed without showing any tendency to pass into a colloidal state. The metal is finally filtered and dried in a vacuum over sulfuric acid. Great care must be taken in the subsequent admission of air as the metal readily becomes incandescent owing to adsorption of oxygen.

Adams Platinum Oxide (by Adams et al.).[148] In a porcelain casserole is prepared a solution of 3.5 g of chloroplatinic acid in 10 ml of water, and to this is added 35 g of sodium nitrate.The mixture is evaporated to dryness while stirring with a glass rod. The temperature is then raised to 350–370°C within ~10 min. Fusion takes place, brown oxides of nitrogen are evolved, and a precipitate of brown platinum oxide gradually separates. After 15 min, when the temperature has reached about 400°C, the evolution of gas has gently decreased. After 20 min the temperature should be 500–550°C. The temperature is held until about 30 min have elapsed, when the fusion should be complete. The mass is allowed to cool and is then treated with 50 ml of water.The brown precipitate settles to the bottom and can be washed by decantation once or twice, then filtered, and washed until practically free from nitrates. If the precipitate becomes colloidal, it is better to stop washing immediately at that stage. The oxide is either used directly or dried in a desiccator. The yield is 1.57–1.65 g (95–100% of the theoretical amount).

1.5.1.2 Colloidal Platinum. Colloidal solutions (hydrosols) of platinum metals, such as produced by Bredig's method or by chemical reductions, are unstable unless suitable colloidal substances (protective colloids) are present. Paal prepared a colloidal platinum catalyst by reducing chloroplatinic acid with hydrazine in the presence of sodium lysalbate, prepared by treating egg albumin with sodium hydroxide.[149,150] The black colloidal solution was then dialyzed to remove electrolytes. The colloidal solutions prepared with sodium lysalbate, or the similar protalbate, as protective colloid, suffer from the disadvantage that it is coagulated by acids. By using gum arabic as protective colloid, Skita obtained a colloidal solution which was stable in acidic medium.[151] A colloidal platinum catalyst is prepared simply by reducing the hydrosols of platinum with hydrogen in the presence of gum arabic and the substrate to be hydrogenated. In the absence of a substrate, the hydrosols were reduced with addition of a trace of previously prepared colloidal metal (Skita's inoculation or germ method). Alternatively, stable hydrosols are prepared by boiling a solution of chloroplatinic acid with the theoretical amount of sodium hydroxide or sodium carbonate solution and a little gum arabic. The product is dialyzed to eliminate chloride and carbonate, and evaporated cautiously, finishing in vacuum. The hydroxide colloidal solution thus prepared may be used as an efficient catalyst in acid medium. Colloidal catalysts of the platinum metals have also been

prepared using various protective colloids such as gluten,[152] silicic acid,[153] starch,[154] and synthetic polymers.[155–157] However, colloidal catalysts have not found wide use because of their instability, the difficulty in the separation of substrate, and limited suitable solvents and reaction conditions for them.

1.5.1.3 Supported Platinum. Supported platinum catalysts have been prepared usually by impregnation method, using various supports such as charcoal,[158] asbestos,[159] silica,[160] alumina,[161] and silica–alumina,[162] or by ion-exchange method with silica, silica-alumina, and zeolites, using cationic platinum salts.[163,164]

Maxted and co-workers investigated the effects of various oxide supports on the activity of resulting platinum catalysts.[165,166] To a known amount of each support suspended in 10 ml of water was added the calculated volume of a 1% aqueous solution of chloroplatinic acid and an excess of 40% aqueous formaldehyde. After diluting the solution with about 75 ml of water, the system was boiled for 20 min. In this way, a fixed amount of platinum (0.00625 g) was deposited on varying amounts of different supports, and the activity of the preparations was determined for the hydrogenation of cyclohexene in absolute ethanol at 20°C and atmospheric pressure. In all cases the activity of the catalyst with the fixed amount of platinum first rose to a peak value and then fell with increasing amount of the support. The maximum activities, which occurred at different ratios of support to platinum for each support used, decreased in the order $ZrO_2 > ThO_2 > Cr_2O_3 > CeO_2 > ThO_2 \cdot 2Cr_2O_3 > MgO$. Ziconia and thoria with low surface areas (5.85 and 4.5 $m^2 \cdot g^{-1}$, respectively) have been found to be highly effective as supports; the peak activities were about 16 and 12 times that of unsupported platinum at approximately 0.31 and 0.2% loading of platinum on the support, respectively. An alumina with a small mean pore radius (2.1 nm) was as effective as the zirconia with a large mean pore radius (38.2 nm) in the hydrogenation of cyclohexene, whereas, in the hydrogenation of ethyl crotonate, the activity at the maximum decreased to a greater extent with the alumina than with the zirconia with which a catalyst 16 times as active as unsupported platinum was obtained. These results have suggested that the pore factor is important, especially if the supported catalyst is used for the hydrogenation of a large molecule.

Pt–C (by Kaffer).[158] To 10–12 g of active carbon mixed well with water is added an aqueous solution of the calculated amount of chloroplatinic acid. The mixture is warmed on a water bath for a few hours at 50°C. After cooling, a concentrated sodium carbonate solution is added until the mixture becomes alkaline. Then a hydrazine hydrate solution is added drop by drop under stirring. Whether the amount of hydrazine is sufficient to reduce the chloroplatinic acid can be readily determined by the decoloration of a permanganate solution. The platinum–carbon suspension is further warmed for 1–2 h on a water bath, filtered, and washed with hot water until the washing is free from chloride and alkali. After dried as fully as possible between filterpapers, the catalyst is dried for half a day over calcium chloride in vacuum. Kaffer used a 10% Pt–C thus prepared for the dehydrogenation of decalin and found it much more effective than Pt–asbestos by Zelinsky. Newhall used a 5% Pt–C by Kaffer for

the hydrogenation of limonene at room temperature and a low hydrogen pressure without using hydrazine in the final stage of the preparation[167] (see eq. 3.11).

$Pt–SiO_2$. Platinum catalysts supported on silica gel may be prepared either by impregnating chloroplatinic acid to silica gel followed by reduction with formaldehyde[160] or hydrogen, or by ion exchange of cationic tetraammine platinum(II) ion, $Pt[(NH_3)_4]^{2+}$, with the cationic center of silica gel followed by reduction with hydrogen.[164] Benesi et al. have shown that more highly dispersed platinum (average 1.5-nm crystallites) supported on silica is prepared by the ion-exchange method than that by the impregnation method (1.5–4.5-nm crystallites). In the case of impregnated preparations the atomic ratio of adsorbed hydrogen to platinum decreased at higher platinum contents but increased almost linearly with increasing platinum up to 4.5% in the case of the ion-exchanged preparations.[163]

1.5.2 Palladium

In principle, the same methods used for the preparation of platinum catalysts may be applied for palladium catalysts. When palladium chloride is used as a starting material, it is usually dissolved into an aqueous solution as chloropalladic acid by adding hydrochloric acid prior to reduction or formation of precipitates. Unsupported and supported palladium catalysts have been prepared by reduction of palladium salts with alkaline formaldehyde,[139,168] sodium formate,[169] hydrazine,[150] hydrogen,[170,171] sodium borohydride,[146,172] or sodium hydride-*t*-AmOH,[173] or by reduction of palladium hydroxide[174,175] or palladium oxide[176] with hydrogen.

Palladium Black (by Zelinsky and Glinka).[169] One liter of a 2% solution of palladiumammonium chloride is mixed with 24 g of formic acid, and 50 ml of 20% potassium hydroxide solution is added to the solution on warming. With continuing warming a violent reaction occurs to give palladium black as precipitates, and the supernatant liquid becomes clear. The palladium black is filtered, washed well until no chloride ion is detected in the washing, and then dried in a desiccator over sulfuric acid.

Palladium Black from Palladium Hydroxide.[175] To a 2% aqueous solution of palladium chloride heated to 90–95°C is added with stirring about 5% lithium hydroxide solution drop by drop until the pH of the solution becomes 7.5–7.8 and no more changes occur on further standing. The brown palladium hydroxide thus precipitated is washed with hot distilled water on a filter paper. If the filtrate becomes colloidal, the washing is stopped immediately. The solid is dried between filter papers, and then in a desiccator. A finely ground powder of palladium hydroxide is suspended in water and reduced to the black form at room temperature and atmospheric pressure in a shaking apparatus. As soon as black precipitates are formed and the supernatant water becomes clean, the reduction is interrupted, and the palldium black is washed with water on a filter paper or in an Erlenmeyer flask by decantation. The reduction and washing process is repeated until the pH of the solution after the reduction

becomes almost the same as that of the water added prior to reduction. The palladium black thus prepared behaves in the same way as a palladium black formed from its vapor in the acetal formation and hydrogenation of 4-methylcyclohexanone in ethanol.[147]

Unsupported palladium catalysts are often unstable in use at elevated temperatures and/or high hydrogen pressures. Yada et al. obtained a highly stable palladium black by precipitating palladium hydroxide from palladium chloride solution with an aqueous sodium aluminate instead of sodium hydroxide.[177] The palladium catalyst obtained by reduction of the palladium hydroxide prepared with a 1*M* sodium aluminate solution at pH 10, in the same way as described above, kept a high surface area of 139 $m^2 \cdot g^{-1}$ even after the reduction at 200°C in a flow of hydrogen, compared to only 2.0 $m^2 \cdot g^{-1}$ with the catalyst prepared using a sodium hydroxide solution as precipitant. The thermally stable catalyst was found to contain 13 ppm of sodium and 1400 ppm (0.14%) of aluminum.

Palladium Oxide (by Shriner and Adams[176a]).[176b] In a 350-ml casserole, 2.2 g (0.02 mol) of palladium metal is dissolved in a small amount of aqua regia, and the solution is treated with 55 g of sodium nitrate and enough distilled water to make a thick paste. The substances are thoroughly mixed and then heated gently to drive off the water. The heating is increased until the mixture melts (about 270–280°C) and continued cautiously. Just above the melting point the mixture must be stirred and heated carefully as oxides of nitrogen are evolved and foaming occurs. After the evolution of gases is nearly complete (about 5 min), the full flame of a Bunsen burner is applied for about 10 min. The cooled mass is digested with about 200 ml of distilled water until the sodium salts are completely dissolved, the dark brown precipitate of palladium oxide is filtered, and is washed thoroughly with 1% sodium nitrate solution. The oxide must not be washed with pure water since it tends to become colloidal. After drying in a vacuum desiccator the palladium oxide weighs 2.3–2.4 g (91–95% of the theoretical amount). The oxide was used without prereduction in the hydrogenation of furan to tetrahydrofuran at room temperature (RT) and 0.7 MPa H_2 with a lag of about 10 min.

Pd–$BaSO_4$ (5% Pd) (Procedure A by Mozingo).[178] A solution of 8.2 g of palladium chloride (0.046 mol) in 20 ml (0.24 mol) of concentrated hydrochloric acid and 50 ml of water is prepared. To a rapidly stirred, hot (80°C) solution of 126.2 g (0.4 mol) of barium hydroxide octahydrate in 1.2 liters of distilled water contained in a 4-liter beaker is added all at once 120 ml (0.36 mol) of 3*M* sulfuric acid. More 3*M* sulfuric acid is added to make the suspension just acid to litmus. To this hot barium sulfate suspension are added the palladium solution and 8 ml (0.1 mol) of 37% formaldehyde solution. The suspension is then made slightly alkaline to litmus with 30% sodium hydroxide solution, with constant stirring maintained. The suspension is stirred 5 min longer, and then the catalyst is allowed to settle. The clear supernatant liquid is decanted and replaced by water, and the catalyst is resuspended. The catalyst is washed 8–10 times by decantation, collected on a glass funnel, washed with 250 ml

of water in five portions, and then dried in an oven at 80°C. The catalyst (93–98 g) is powdered and stored in a tightly closed bottle.

Pd-$BaSO_4$ catalyst has often been used for selective hydrogenations such as the Rosenmund reduction (Chapter 13) and the hydrogenation of acetylenic to ethylenic compounds (see, e.g., Chapter 4, eqs. 4.8–4.10).

Pd–C (5% Pd) (Procedure B by Mozingo).[178] A suspension of 93 g of nitric acid–washed Darco G-60 (or Norit, or other carbons) in 1.2 liters of water contained in a 4-liter beaker is heated to 80°C. To this is added a solution of 8.2 g (0.046 mol) of palladium chloride in 20 ml (0.24 mol) of concentrated hydrochloric acid and 50 ml of water, and then 8 ml (0.1 mol) of 37% formaldehyde solution. The suspension is made slightly alkaline to litmus with 30% sodium hydroxide solution, and constant stirring is maintained. The suspension is stirred 5 min longer. The catalyst is collected on a filter, then washed 10 times with 250-ml portions of water. After removal of as much water as possible by filtration, the filter cake is dried, first in air at room temperature, and then over potassium hydroxide in a desiccator. The dry catalyst (93–98 g) is stored in a tightly closed bottle.

Pd–C (5% Pd) (Procedure C by Mozingo).[178,179] A solution of 8.2 g (0.046 mol) of palladium chloride in 20 ml of concentrated hydrochloric acid and 50 ml of water is prepared. The solution is diluted with 140 ml of water and poured over 92 g of nitric acid–washed Darco G-60 in a 20-cm evaporating dish. After the palladium chloride solution has been thoroughly mixed with the carbon, the whole mixture is dried, first on a steam bath and then on an oven at 100°C, with occasional mixing until completely dry. The mass (98–100 g) is powdered and stored in a closed bottle. The required quantity of the $PdCl_2$–C is transferred to a hydrogenation bottle and reduced with hydrogen in the solvent to be used for hydrogenation. When no more hydrogen is absorbed, the catalyst is collected and washed with more of the solvent to remove the hydrogen chloride, and then returned to the hydrogenation bottle. Alternatively, the $PdCl_2$–C is reduced with hydrogen in water, and the catalyst is filtered, washed, dried carefully, and kept in vacuo over sulfuric acid until used.[179]

Pd–C (10% Pd) (Procedure D by Mozingo).[178,180] A solution of 8.33 g (0.0472 mol) of palladium chloride in 5.5 ml (~0.066 mol) of concentrated hydrochloric acid and 40 ml of water is prepared by heating the mixture on a water bath. The resulting solution is poured into a solution of 135 g of sodium acetate trihydrate (0.99 mol) in 500 ml of water contained in a 1-liter reduction bottle. Then 45 g of Norit is added, and the mixture is hydrogenated until absorption ceases after 1–2 h. The catalyst is collected on a Buchner funnel and washed with 2 liters of water in five portions. The filter cake, after removal of most of water, is dried in air and then in a desiccator over calcium chloride. The catalyst (48–50 g) is stored, after being powdered, in a tightly closed bottle.

$Pd(OH)_2$–C (by Pearlman) (20% Pd)

Method A.[174a] Palladium chloride (100 g, 0.565 mol), carbon (Darco G-60) (240 g), and deionized water (2 liters) are mixed and rapidly stirred while being heated to 80°C. Lithium hydroxide, $LiOH \cdot H_2O$, (50 g, 1.19 mol) dissolved in water (200 ml), is added all at once and the heating is stopped. The mixture is stirred overnight, and washed with 0.5 v/v% aqueous acetic acid (2 liters). The filter cake is sucked as dry as possible and dried in vacuo at 60°C. The yield is 300–320 g.

Method B.[174b] A rapidly stirred mixture of 68.6 g of activated charcoal (Mallinckrodt) and 30 g (0.17 mol) of palladium chloride in 43 ml (0.516 mol) of concentrated hydrochloric acid and 570 ml of water is heated to 60°C. To the mixture is added 31 g (0.775 mol) of sodium hydroxide pellets at such a rate that the temperature does not exceed 80°C. The mixture is then treated with 6.6 g (0.0785 mol) of solid sodium bicarbonate and stirred for 12 h. The catalyst is filtered, and then washed with 430 ml of water and 8.6 ml of glacial acetic acid. The catalyst is dried in vacuo at 65°C, and stored under nitrogen.

The Pd–C catalyst prepared in an acidic medium often shows a behavior different from that of a Pd–C catalyst prepared in an alkaline medium, even after both catalysts have been washed repeatedly with distilled water. The former catalyst has been designated as Pd–C A and the latter, Pd–C B (see, e.g., Section 11.2.2 and Table 13.1). The Pd–C prepared by the Mozingo's procedure B is considered to be Pd–C B, while the Pd–C prepared by Mozingo's procedure C is a typical example of Pd–C A. It should be noted that direct addition of methanol or ethanol to metallic palladium catalysts that have been stored in air results in deactivation. To avoid such deactivation, the catalyst should be pretreated with hydrogen in an inert solvent such as cyclohexane, which is then replaced by methanol or ethanol (see Table 13.6, and also Table 5.5). $Pd(OH)_2$–C or $PdCl_2$–C does not appear to be susceptible to such a deactivation on contact with the alcohols. Rylander and Karpenko observed that the catalytic activity on the basis of the unit weight of palladium that is supported on carbon increased with decreasing concentration of metal in the concentration range from 30 to 1%.[181] The relative rate for varying concentration (see figures in parentheses) of palladium in the hydrogenation of nitrobenzene in acetic acid at room temperature and atmospheric pressure was 1.0 (30%), 1.2 (10%), 1.8 (5%), 3.5 (3%), and 7.6 (1%).

Lead-Poisoned Pd–$CaCO_3$ (Lindlar Catalyst).[182] Palladium chloride (1.48 g, 0.0083 mol) is placed in a 10-ml Erlenmeyer flask, and 3.6 ml (0.043 mol) of 37% hydrochloric acid is added. The flask is shaken at about 30°C until the palladium chloride is dissolved. The chloropalladic acid solution is transferred to a 150-ml beaker with 45 ml of distilled water. The pH of the solution is brought to 4.0–4.5 by slow addition of aqueous 3*M* sodium hydroxide. The solution is diluted to approximately 100 ml and placed in a 200- or 250-ml three-necked, round-bottomed flask equipped with a mechanical stirrer and a thermometer. Precipitated calcium carbonate (18 g) is added. The well-stirred suspension is heated to 75–85°C and held

at this temperature until all the palladium has precipitated, as indicated by loss of color from the solution; this takes about 15 min. With the mixture still at 75–85°C, 6.0 ml of sodium formate solution (about 0.7*M*) is added with rapid stirring. During the addition CO_2 escapes and the catalyst turns from brown to gray. An additional 4.5 ml of the sodium formate solution is added, and the reduction is completed by stirring the mixture at 75–85°C for 40 min. The catalyst is separated on a 10-cm Buchner funnel and washed with eight 65-ml portions of water. The moist catalyst is placed in a 200- or 250-ml round-bottomed flask equipped as described above. Water (60 ml) and 18 ml of a 7.7% solution of lead acetate are added. The slurry is stirred and heated at 75–85°C for 45 min. The catalyst is separated, washed with four 50-ml portions of water, and then dried in an oven at 60–70°C. The dried catalyst, a dark gray powder, weighs 19–19.5 g (4.55–4.67% Pd).

The Lindlar catalyst was first described by Lindlar in 1952 and used with a small amount of quinoline for the selective hydrogenation of a conjugated enyne to the conjugated diene in the synthesis of an intermediate leading to vitamin A.[183] In his original procedure, palladium oxide or hydroxide on calcium carbonate was reduced to metal with hydrogen. It appears that the improved method using sodium formate as a reducing agent as described above gives a catalyst with more uniformly dispersed metal on the support, as judged from the color of the resulting catalyst. The Lindlar catalyst has proved to be highly selective for the hydrogenation of alkynes to alkenes (see Section 4.1). It should be noted that the high selectivity of Lindlar catalyst is decreased when used in a hydroxylic solvent.[182] The treatment of the Pd–$CaCO_3$ with the lead acetate solution should also be modified to avoid poisoning the catalyst too strongly, by adjusting the concentration of the solution, depending on the substrate to be hydrogenated (see, e.g., eqs. 4.3 and 4.4).[184]

Maxted and Ali studied the effects of various oxide supports on palladium in the hydrogenation of cyclohexene in ethanol at 20°C and atmospheric hydrogen pressure.[185] The catalysts were prepared by reduction of palladium chloride with formaldehyde and sodium carbonate in boiling aqueous solution in the presence of the supports. As in the case with platinum catalysts, the activity of the supported catalyst, containing a constant amount of palladium, first rose to a peak value and subsequently fell as the amount of the support was further increased. The activity of the supported catalyst at the peak points amounted to about 24 times the value for unsupported catalyst with ZrO_2 and ThO_2 and to about 22 times with Al_2O_3 and TiO_2. ZrO_2^{I} and $Al_2O_3^{I}$ with larger surface areas (11.9 and 160.6 $m^2 \cdot g^{-1}$, respectively) gave the catalysts with greater peak activities than ZrO_2^{II} and $Al_2O_3^{II}$ with smaller surface areas (5.1 and 16.6 $m^2 \cdot g^{-1}$, respectively). The amount of the support required for the accommodation of palladium at the peak ratio (e.g., 2.5 g for 6 mg Pd with ZrO_2^{I}) was far more than would be required even for a monolayer of palladium (0.2532 g with ZrO_2^{I}).

1.5.3 Ruthenium

Since ruthenium catalysts were shown to be highly active and selective for the hydrogenation of aromatic amines by Behr et al.,[186a] Whitman,[186b] and Barkdoll et al.,[93] the usefulness of ruthenium as hydrogenation catalysts has been recognized by many

other investigators in various hydrogenations.[187] The hydrogenation of aromatic amines over ruthenium catalysts usually proceeds at much lower temperatures and pressures than over nickel and cobalt catalysts (see Section 11.5). Ruthenium dioxide has often been used as a catalyst for this reaction without any details in its preparation.[93,188] It appears that the excellent nature of the ruthenium dioxide is likely to be associated with alkaline substances contained in it. Ruthenium hydroxide has also been shown to be an effective catalyst in the hydrogenation of various aromatic compounds.[187,189] The ruthenium hydroxide prepared from ruthenium chloride and alkali tends to readily occlude alkali before all the chloride has been transformed into the hydroxide, probably because of a strong amphoteric property of the hydroxide. It is probable that the high selectivity of ruthenium catalysts in the hydrogenation of benzyl–oxygen compounds is related to trace amounts of alkali remaining in the catalysts (see Table 11.14). It is also noted that ruthenium, along with osmium and in contrast to the other platinum metals, can be transformed into solution by fusion with, for instance, sodium peroxide, which oxidizes ruthenium to soluble sodium ruthenate(VI), Na_2RuO_4. Pichler's ruthenium dioxide was prepared by the reduction of potassium ruthenate with methanol.[190]

Ruthenium Dioxide (by Pichler).[190] A mixture of 1 g of ruthenium powder, 10 g of potassium hydroxide, and 1 g of potassium nitrate is fused in a silver (or a nickel) crucible. It is recommended that the potassium nitrate be added not simultaneously but in portion after portion. In 1–2 h the fusion is complete. After cooling, the mass is dissolved with water into a solution. The dark red solution of potassium ruthenate is heated to boiling, and methanol is added to this dropwise. Immediately after the first drop of methanol has been added, the reduction of the ruthenate to ruthenium dioxide takes place and the reduction is completed in a few minutes. After leaving the precipitate for 1–2 h, the precipitate is collected on a glass filter, washed 7 times with a dilute nitric acid solution and then 18 times with distilled water, and dried at 110°C for 24 h in a desiccator. Pichler's dioxide thus prepared does not show any distinct diffraction patterns corresponding to the oxide of ruthenium and is partly soluble into hot concentrated hydrochloric acid. These facts suggest that Pichler's dioxide is a mixture of the oxide and the hydroxide of ruthenium.[191]

Ruthenium Hydroxide.[187,192] To an ~1% aqueous solution of ruthenium chloride heated to 90–95°C is added an ~5% lithium hydroxide solution dropwise under vigorous stirring until the pH of the supernatant liquid becomes 7.5–7.8. Addition of a few drops of the lithium hydroxide solution is usually necessary to prevent the pH of the liquid from becoming more acidic on continued stirring for a further 10–20 min. The black precipitate formed is collected on a filter paper, washed repeatedly with hot distilled water until the filtrate becomes almost neutral, and then dried in vacuo at room temperature. The dried hydroxide is pulverized into fine particles and can be used for hydrogenation at elevated temperatures and pressures without prereduction.

Ruthenium Black from Ruthenium Hydroxide. The ruthenium hydroxide (1 g) prepared as described above is suspended in 100 ml of water in a hydrogenation bottle and reduced with atmospheric pressure of hydrogen at room temperature or 40–50°C until black precipitates of ruthenium are separated out. The supernatant liquid, which is not always clear but is often colored brown, is decanted and the precipitate is washed thoroughly with distilled water. To obtain a catalyst with lesser amounts of alkaline or acidic impurities, the reduction–washing process is repeated until the supernatant liquid becomes neutral.

$Ru(OH)_3$(10% Ru)–$Pd(OH)_2$(0.1% Pd)–C.[174a] $RuCl_3 \cdot 3H_2O$ (52.4 g), $PdCl_2$ (0.34 g), carbon (Darco G-60) (180 g), and water (2 liter) are mixed, rapidly stirred, and heated to 80°C. $LiOH \cdot H_2O$ (27 g) dissolved in water (100 ml) is added all at once and the heating stopped. The mixture is stirred overnight, filtered, and washed with a liter of 0.5 v/v% aqueous acetic acid. The product is dried in vacuo at 65°C. The yield is 202–211 g. The palladium hydroxide is incorporated in order to shorten the reduction time of the ruthenium hydroxide.

Reduced ruthenium catalysts stored in air are usually oxidized on the surface and must be activated by prereduction with hydrogen for 1–2 h before use for hydrogenations at a low temperature and pressure. In contrast for platinum and palladium catalysts, organic as well as inorganic acids strongly poison the ruthenium catalyzed hydrogenation. Thus acetic acid should not be added or used as solvent for the hydrogenations over ruthenium, particularly under mild conditions.

1.5.4 Rhodium

Beeck was the first to note that rhodium is the most active of the transition metals for the hydrogenation of ethylene, as observed with evaporated metal films.[193] Later, rhodium or rhodium-based catalysts were shown to be highly active for the hydrogenation of aromatic nucleus under very mild conditions.[194,195] Over Rh–Al_2O_3 and Rh–Pt oxide catalysts, aromatic compounds with hydrogenolyzable oxygen functions have been hydrogenated to the corresponding saturated compounds with little loss of the oxygen groups, when used with addition of acetic acid or even in acetic acid[195–197] (see, e.g., Sections 11.2.3 and 11.3).

$Rh(OH)_3$, Rh Black, and $Rh(OH)_3$(10% Rh)–$Pd(OH)_2$(0.1% Pd)–C. These catalysts can be prepared exactly in the same way as for the preparation of the corresponding ruthenium catalysts.

7:3 Rh–Pt Oxide (Nishimura Catalyst).[198] A solution of 0.75 g of rhodium chloride $RhCl_3 \cdot 3H_2O$ (0.30 g Rh) and 0.35 g of hexachloroplatinic acid $H_2PtCl_6 \cdot 6H_2O$ (0.13 g Pt) is mixed with 20 g of sodium nitrate in a 80-ml porcelain casserole with addition of a small amount of water. On stirring with a glass rod, the mixture is gently heated to dryness and then heated strongly to fuse. After a violent evolution of the oxides of nitrogen has almost subsided, the temperature is raised to 460–480°C

and kept at that temperature for about 10 min. After cooling to room temperature, the solidified mass is rinsed in water. The solid is collected, washed with 100 ml of 0.5% aqueous sodium nitrate, and then dried over calcium chloride. The yield (0.665 g) is quantitative on the basis of the metal content (65%) of the oxide. The mixed oxide can be reduced to the metal with hydrogen in 24 min in acetic acid at 30°C and atmospheric hydrogen pressure, compared to 3.5 h in the case of pure rhodium oxide. The mixed rhodium–platinum catalysts thus prepared and containing 70–90% rhodium have been found to be more active and selective than the pure rhodium catalyst prepared in the same way in the hydrogenation of toluene and acetophenone at 30°C and atmospheric pressure. The catalysts containing 30% or more of platinum can be dissolved completely with aqua regia. Similar synergistic effects of rhodium and platinum have also been observed with rhodium–platinum on carbon catalysts (5% metal) in the hydrogenation of phenol and benzoic acid (see Sections 11.2 and 11.4).[135]

Rhodium catalysts tend to be poisoned by halogen acids more strongly than palladium and platinum, especially in nonhydroxylic solvents.

Colloidal Rhodium. Colloidal dispersions of rhodium have been prepared by reducing rhodium salts or hydroxide with hydrogen in the presence of poly(vinyl alcohol),[155] with refluxing methanol–water in the presence of poly(vinyl alcohol)[199] or poly(vinylpyrrolidone),[200] and with refluxing methanol/sodium hydroxide in the presence of poly(vinylpyrrolidone). As an example, the last-mentioned procedure, which has given a colloidal rhodium of highest dispersion (average diameter of 0.9 nm), is described; $RhCl_3 \cdot 3H_2O$ (8.8 mg, 0.033 mmol) and poly(vinylpyrrolidone) (150 mg) (degree of polymerization 3250) are dissolved separately in two portions of methanol (22.5 ml for each). Both solutions are combined and refluxed for 30 min. A methanol solution (5 ml) of sodium hydroxide (6.7 mg, 0.17 mmol) is added drop by drop to the solution under reflux, resulting in rapid color change to dark brown, indicating the formation of colloidal rhodium. With further refluxing for 10 min, a dark brown solution of colloidal rhodium, which has been stable on standing in air for 9 days, is obtained.

1.5.5 Osmium

Compared to the other platinum metals, osmium has found only limited use in catalytic hydrogenation. This may be due to its high price as well as to its rather mild catalytic activity in hydrogenation. However, some selective hydrogenations that are successful over osmium as catalyst have been known. For example, 5% Os–C has been shown to be highly selective for the hydrogenation of α,β-unsaturated aldehydes to allylic alcohols even without any additives (see eq. 5.26).[201] Over osmium black 1,2-dimethylcyclohexene and *o*-xylene are hydrogenated to *cis*-1,2-dimethylcyclohexane with high stereoselectivity.[202] Osmium black is readily prepared by reduction of osmium tetroxide with hydrogen.

Osmium Black.[203] In an autoclave with a teflon or glass stirrer and a teflon or glass cylinder installed in it is placed osmium tetroxide OsO_4 (1 g) and water or isopropyl alcohol (15–20 ml). The solution is reduced at 90°C and 6 MPa H_2 for 40 min. The catalyst is dried and stored in a sealed bottle under an inert gas in a refrigerator, since metallic osmium tends to be oxidized with air to form gaseous products.

1.5.6 Iridium

Iridium,[204,205] together with osmium, has been not widely used in catalytic hydrogenation. Recently, however, iridium or iridium-based catalysts have been shown to be effective in various hydrogenations, such as in selective hydrogenation of α,β-unsaturated aldehydes to allylic alcohols (Section 5.2), of aromatic nitro compounds to the corresponding hydroxylamines (Section 9.3.6), of halonitrobenzenes to haloanilines without loss of halogen (Section 9.3.2), and in the stereoselective hydrogenation of carbon to carbon double bonds (see, e.g., eqs. 3.25–3.27 and Table 11.5).[204,205] Unsupported iridium catalysts have been prepared by reducing an iridium oxide of Adams type at 165°C under a stream of hydrogen[206] or by reducing iridium hydroxide, prepared by addition of lithium hydroxide to an aqueous solution of iridium(III) chloride, at 80–90°C and 8 MPa H_2.[204] Unsupported and supported iridium catalysts may also be prepared by reduction of iridium(IV) chloride with sodium borohydride.[207] It is noted that the catalytic activity of deactivated iridium can be almost completely regenerated by treatment with concentrated nitric acid.[205]

Iridium Black.[204] Iridium(III) hydroxide is reduced in water at 90°C and 8 MPa H_2 for 40 min, in the same way as in the preparation of osmium black. The iridium(III) hydroxide is prepared by adding an aqueous lithium hydroxide solution dropwise to an ~1% aqueous solution of water-soluble iridium(III) chloride, $IrCl_3 \cdot 3H_2O$, at 90–95°C until the pH of the solution becomes 7.5–7.8 under stirring. By keeping the solution at the same temperature under stirring, the precipitate of iridium(III) hydroxide is separated out from its colloidal solution. The precipitate is collected, washed repeatedly with hot water, and then dried in vacuo.

1.6 RHENIUM CATALYSTS

Rhenium catalysts[208] had found little attention until their attractive catalytic properties in hydrogenation have been revealed by a systematic study by Broadbent and coworkers beginning in 1951[208] (the first paper appeared in 1954[209]). Some characteristic properties of rhenium catalysts are seen, such as in the selective hydrogenation of α,β-unsaturated aldehydes to unsaturated alcohols (see eq. 5.27), the hydrogenation of carboxylic acids to alcohols (see eqs. 10.3 and 10.4), and the hydrogenation of carboxamides to amines (see eq.10.43). Rhenium also plays an important role, together with platinum, in a reforming process known as *rheniforming*.[210] Ammonium perrhenate NH_4ReO_4 or rhenium heptoxide Re_2O_7 are usual convenient starting materials for the preparation of the catalysts.

Rhenium Black. An active rhenium black may be prepared by reduction of rhenium heptoxide in an appropriate solvent (anhydrous ethanol, anhydrous dioxane, glacial acetic acid, or water) at elevated temperatures (120–220°C) and pressures (15–21 MPa H_2), or in situ in the presence of the substrate to be hydrogenated.[211] In a typical procedure, 5 g of rhenium heptoxide, along with 150 ml of purified dioxane, is placed in a glass-lined or glass-bottle-installed autoclave and reduced at 120°C and 13.7 MPa H_2 for 4 h.[212] After cooling the rhenium black is isolated by filtration or centrifugation, then washed several times and stored under the solvent to be used for subsequent hydrogenations, or is dried in vacuo and stored under nitrogen.

Rhenium Sulfides and Selenides.[208,209] These catalysts are characterized by their outstanding resistance to poisoning and minimal tendency to cause the hydrogenolysis of carbon–sulfur bonds than the base metal sulfides. Rhenium heptasulfide is easily prepared from boiling 6*M* hydrochloric acid solutions of perrhenate with hydrogen sulfide. It has been noted that occasional exposure of the dried, powdered catalyst to the atmosphere is not deleterious.

1.7 THE OXIDE AND SULFIDE CATALYSTS OF TRANSITION METALS OTHER THAN RHENIUM

The transition metal oxides or sulfides catalyze various reactions related to hydrogenation and hydrogenolysis, although at relatively high temperatures and pressures. Compared to metallic catalysts, they are resistant to poisons and stable at high temperatures. Industrially, they are often used as mixed oxides or sulfides. For example, the most common catalyst used in the hydrodesulfurization process is a mixture of cobalt and molybdenum oxides supported on γ-alumina, which is sulfided before use. Nickel–molybdenum and nickel–tungsten oxides are also known as effective catalyst systems for this process.[213] Molybdenum sulfides are active for the hydrogenolysis of aldehydes, ketones, phenols, and carboxylic acids to the corresponding hydrocarbons,[214] and also effective for the hydrogenolysis of sulfur-containing compounds (see, e.g., eqs. 13.96, 13.97, and 13.99).

The sulfides of the platinum metals have been found to be active at lower temperatures than required for the base metal sulfides. They are insensitive to poisons and have proved particularly useful for hydrogenations in the presence of impurities, for the hydrogenation of sulfur-containing compounds, and for selective hydrogenation of halogen-containing aromatic nitro compounds (Section 9.3.2).[215]

Molybdenum Oxides. Molybdenum oxide catalysts are prepared by the addition of hydrochloric acid to an ammoniacal solution of molybdic acid or ammonium molybdate. By heating to 400–500°C the molybdate is decomposed to the oxide.[216] MoO_3 is reduced to MoO_2 in a stream of hydrogen at 300–400°C.

Molybdenum Sulfides.[217] MoS_3: to a solution of 100 g (0.081 mol) of ammonium molybdate(VI), $(NH_4)_6Mo_7O_{24} \cdot 4H_2O$, dissolved in 300 ml of distilled water, is added

1 liter of aqueous solution of ammonia (*d* = 0.94), hydrogen sulfide gas is introduced into the solution until saturated under cooling, and the solution is left overnight. The crystals of ammonium thiomolybdate thus formed are collected. An aqueous solution of the thiomolybdate is acidified, with stirring, with a dilute sulfuric acid solution. After further stirring for 1 h, the suspension is left overnight. The precipitate is well washed with water by decantation, filtered off under suction, and then dried at 70–80°C. MoS_2 is obtained by reduction of MoS_3 with hydrogen at 350–380°C and 6 MPa for 6 h.

Platinum Metal Sulfides. These are usually prepared by passing hydrogen sulfide gas into an acid solution of metal chlorides or by heating fine metals in a stream of hydrogen sulfide.[218]

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CHAPTER 2

Reactors and Reaction Conditions

2.1 REACTORS

Catalytic hydrogenations are performed in either the gas or liquid phase in reactors for either flow or batch systems. The physical form of a catalyst is determined by the reactor in which it is used. Usually coarse particles or monolithic structures are used in fixed-bed reactors, while fine particles are preferred in fluidized-bed, bubbling column, and batch reactors. The reactors for batch systems are usually equipped with an efficient stirring device. Ultrasonic irradiation has been reported to be effective for activating catalysts, preparing active catalysts, or accelerating hydrogenations.[1] Komarewsky et al. give a comprehensive article on various reactors for atmospheric, subatmospheric and superatmospheric reactions (Ref. a below). There are many other good descriptions of hydrogenation reactors in the literature, including those listed below.

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2.2 REACTION CONDITIONS

The successful performance of a catalytic hydrogenation depends on a suitable choice of reaction conditions, in particular, the choice of catalyst and its amount, temperature, hydrogen pressure, and solvent. Hydrogenation catalysts are also subject to deactivation or promotion by various substances that are referred to as *inhibitors* (or *poisons*) or *promoters*, respectively. In some cases the impurities of the substrate to be hydrogenated or the product may become a factor that retards the hydrogenation, usually in a later stage of the reaction.

2.2.1 Inhibitors and Poisons

Various types of substances have been known to retard hydrogenation or prevent it from going to completion. These substances are referred to as *inhibitors* or *poisons*, although there appears to be no distinct difference between them. Customarily poisons may be regarded as those substances that exert a marked inhibitory effect when present in small amounts, irrespective of the nature of catalyst and substrate, and cannot be removed easily. Inhibitors usually cause different degrees of deactivation depending on catalyst and substrate, and retard hydrogenation seriously only when present in appreciable concentration. They may be removed often by mere washing.

Maxted classified from a large body of experiments the poisons for metallic catalysts into three classes of substance: (1) the compounds of groups VA and VIA (or groups 15 and 16) elements with at least one unshielded electron pair; (2) heavy metal and metal ions possessing the outer *d* shells, each of which is occupied entirely by at

least one electron; and (3) certain compounds or ions with multiply unsaturated bonds.[2] Typical examples of toxic structures of groups VA and VIA elements are shown in Table 2.1 in comparison with the corresponding nontoxic counterparts. Phosphite and hypophosphite ions show inhibitory effects in spite of their shielded structure. Table 2.2 shows the relationship of poisonous metal ions and the occupied states of their outer *d*-shell electrons. It is noted that Cr^{3+} and Cr^{2+} with two and one unoccupied *d* shells, respectively, are nontoxic, while Mn^{2+} with the *d* shells filled by each one electron is toxic. Typical examples of catalyst poisons belonging to class 3 (listed earlier in this paragraph) are carbon monoxide and cyanide ion.

Besides the poisons of the three classes mentioned above, halide ions or hydrogen halides have often been observed to inhibit hydrogenation, although the degree of inhibition by the halides greatly depends on the catalyst employed, the substrate to be hydrogenated, and particularly on the nature of the halides. Among the halides, iodides have been known to be more poisonous than the other halides. The hydrogenation of *p*-nitrotoluene over 5% Pd–C in 2-propanol–water (4:1) at room temperature and 0.4 MPa H_2 was completely inhibited by 5 mol% of sodium iodide based on *p*-nitrotoluene, similarly as by sodium sulfite, cyanide, sulfide, and bisulfite, while no inhibition was shown by sodium fluoride, chloride, and bromide as well as by sodium nitrate, acetate, carbonate, phosphate, and hydroxide.[3] Sodium iodide was definitely more poisonous than sodium chloride and sodium bromide in the hydrogenation of cinnamic acid over Pd–C in methanol.[4] The hydrogenation of 1-octene and dipropyl ketone over Raney Ni in butanol was depressed by alkali halides in the order KI ≈ NaI > KBr > KCl.[5] The inhibitory effect of iodides on the hydrogenation of the carbonyl group in mesityl oxide in ethanol over Raney Ni or Ni–kieselguhr was in the order $CdI_2 > BaI_2 >$ KI.[6] The poisonous effect of iodides has been applied for depressing overhydrogenation to alcohols in the hydrogenation of benzalacetone, mesityl oxide, and isophorone over Raney Ni.[7]

Ruthenium and rhodium are more susceptible to inhibition by hydrogen halides than are platinum and palladium. Under mild conditions ruthenium is inhibited even by acetic acid, which is generally a good solvent for hydrogenations over rhodium, palladium, and platinum. Hydrogen chloride may become an inhibitor for rhodium-catalyzed hydrogenations. Freifelder has shown that hydrochloric acid is a strong in-

TABLE 2.1 Toxic and Nontoxic Structures of Group VA and VIA Elements

Group	Element	Toxic Compounds	Nontoxic Compounds
VA	N	NH_3, RNH_2, Py, quinoline	NH_4^+, RNH_3^+, PyH^+, quinolinium$^+$
	P	PH_3, R_3P, Ph_3P, HPO_3^{2-}, H_2PO^-	R_3PO, Ph_3PO, PO_4^{3-}
	As	AsH_3	AsO_4^{3-}
VIA	O	O_2, $(OH^-)^a$, $(RO^-)^a$	ROH
	S	H_2S, RSH, R_2S, RSSR, R–SO–R, SO_3^{2-}	$R–SO_2–R$, RSO_3^-, SO_4^{2-}
	Se	H_2Se, R_2Se, SeO_3^{2-}	SeO_4^{2-}

[a]Weakly toxic or nontoxic depending on the nature of catalyst and substrate.

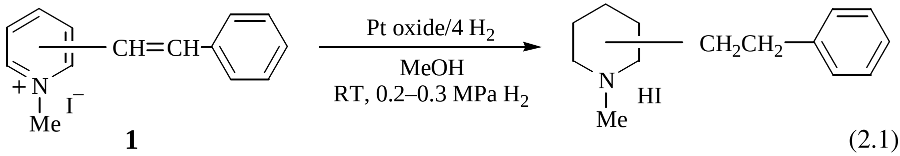
TABLE 2.2 Relationship between the Toxicity of Metal Ions and Outer *d*-Shell Electrons[a]

Periodic Number	Metal Ion	Outer *d*-Shell Electrons					*s*-Shell Electrons	Toxicity
4	K^+, Ca^{2+}	○	○	○	○	○	○	Nontoxic
5	Rb^+, Sr^{2+}, Zr^{4+}	○	○	○	○	○	○	Nontoxic
6	Cs^+, Ba^{2+}, La^{3+}	○	○	○	○	○	○	Nontoxic
6	Ce^{3+}	○	○	○	○	○	○	Nontoxic
7	Th^{4+}	○	○	○	○	○	○	Nontoxic
4	Cr^{3+}	(·)	(·)	(·)	○	○	○	Nontoxic
4	Cr^{2+}	(·)	(·)	(·)	(·)	○	○	Nontoxic
4	Mn^{2+}	(·)	(·)	(·)	(·)	(·)	○	Toxic
4	Fe^{2+}	(:)	(·)	(·)	(·)	(·)	○	Toxic
4	Co^{2+}	(:)	(:)	(·)	(·)	(·)	○	Toxic
4	Ni^{2+}	(:)	(:)	(:)	(·)	(·)	○	Toxic
4	Cu^{2+}	(:)	(:)	(:)	(:)	(·)	○	Toxic
4	Cu^+, Zn^{2+}	(:)	(:)	(:)	(:)	(:)	○	Toxic
5	Ag^+, Cd^{2+}, In^{3+}	(:)	(:)	(:)	(:)	(:)	○	Toxic
6	Au^+, Hg^{2+}	(:)	(:)	(:)	(:)	(:)	○	Toxic
6	Hg^+	(:)	(:)	(:)	(:)	(:)	(·)	Toxic
5	Sn^{2+}	(:)	(:)	(:)	(:)	(:)	(:)	Toxic
6	Tl^+, Pb^{2+}, Bi^{3+}	(:)	(:)	(:)	(:)	(:)	(:)	Toxic

[a] Maxted, E. B. *Adv. Catal.* **1951**, *3*, 129. Reprinted with permission from Academic Press Inc.

hibitor for the hydrogenation of toluene and benzoic acid in methanol over 5% Rh–C or Rh–Al_2O_3, although in rather large quantities (0.1 mol for 0.1 mol of the substrate).[8] Dry hydrogen chloride may become an inhibitor even for platinum and palladium, as observed by Freifelder in the hydrogenation of cyclohexene in absolute ethanol.[9] It is probable that the same degrees of inhibition by hydrogen chloride as observed in the examples given above would be effectuated in much lesser amounts in nonhydroxylic solvents. The amounts of hydrochloric acid required for the stereoselective hydrogenation of unhindered cyclohexanones to the axial alcohols over rhodium black were found to be much smaller in tetrahydrofuran than in isopropyl alcohol (see Table 5.8).[10] The hydrogenation over rhodium was inhibited seriously by the addition of hydrobromic acid. The stereoselectivity of the hydrogenation of 3-oxo-4-ene steroids to 3-oxo-5β steroids over palladium catalyst is increased by addition of hydrochloric acid or, better, by hydrobromic acid.[11] Hydrobromic acid in tetrehydrofuran functions much more effectively than in an alcohol, and it is as effective as or even more effective than the hydrobromic acid in acetic acid.[12] Probably, the amounts of hydrobromic acid required for obtaining an optimal selectivity would be smaller in tetrahydrofuran than in acetic acid. The hydrogenation is slower in the presence of hydrobromic acid than in the presence of hydrochloric acid, and is completely inhibited by the addition of hydroiodic acid. The hydrogenation of 2- or 4-stilbazole methiodides (**1**) to the corresponding phenethylpyperidines (eq. 2.1) proceeded smoothly over platinum oxide

in methanol.[13] In contrast, Pd–C was completely and irreversibly poisoned by small amounts of iodide ion. From the results described above, it may be concluded that the degree of inhibition by hydrogen halides (or halide ions) increases in the order HCl < HBr < < HI and the susceptibility of platinum metals to the inhibition decreases in the order Ru > Rh > Pd > Pt.



(2.1)

The inhibitory effect of nitrogen bases greatly depends on the structure of the bases and the substrate as well as the solvent employed in hydrogenation. Ammonia was a far more strong poison than cyclohexylamine or dicyclohexylamine in the hydrogenation of aniline over ruthenium and rhodium catalysts in isopropyl alcohol, although ruthenium was more resistant to poisoning by ammonia than rhodium.[14] The toxicity of various amines as judged from the results on the hydrogenation of *N*-ethylaniline and pyridine over a rhodium black in isopropyl alcohol (80°C for *N*-ethylaniline and 60°C for pyridine at 7.8 MPa H_2) decreased in the order: NH_3 > > $MeNH_2$ > $EtNH_2$ > Me_2NH > $BuNH_2$ > *t*-$BuNH_2$ > Et_2NH > $EtNHC_6H_{11}$ > Et_3N. The compounds $BuNH_2$, *t*-$BuNH_2$, Et_2NH, Me_3N, and Et_3N had little effect on the hydrogenation of pyridine. According to Maxted, the relative toxicity (the figures in parentheses) of nitrogen bases (CN^- = unity) decreases in the order NH_3 (0.38) > $BuNH_2$ (0.23) > $C_6H_{11}NH_2$ (0.17) > $(C_6H_{11})_2NH$ (0.0028), as compared in the hydrogenation of cyclohexene over a platinum black in cyclohexane (aqueous alcohol for CN^-). Thus the relative toxicity of the nitrogen bases is a function of the molecular size and the steric requirement around the nitrogen atom, rather than their basicity. It is noted that the inhibitory effects of these nitrogen bases can be depressed by the addition of either acid or alkali. Acetic acid appears to be one of preferred solvents for the hydrogenation of aromatic amines with rhodium,[15] palladium,[16] and platinum.[17,18] This is attributed to the fact that acetic acid forms their salts with the product cyclohexylamines that are much more stable than those with the aromatic amines, since cyclohexylamines are definitely more basic (pK_a = 10.5–11) than the parent aromatic amines [pK_a (aniline) = 4.65], and thus depresses the inhibition by the products effectively without much affecting the adsorption of the starting aromatic amines. On the other hand, the inhibitory action of nitrogen bases can also be depressed almost completely by the addition of small amounts of an appropriate alkali (see Section 11.5). The addition of lithium hydroxide has been found to be more effective than any of other alkalies, including sodium hydroxide, potassium hydroxide, and sodium carbonate for the ruthenium-catalyzed hydrogenation of aromatic amines (see eqs. 11.59–11.63).[19]

Excellent examples of the use of nitrogen bases as catalyst poisons are seen in the selective hydrogenation of alkynes to alkenes (see Chapter 4). Quinoline is probably the base that has been most often employed for this purpose. In this selective hydrogenation, the nitrogen base effectively inhibits the hydrogenation of alkenes to alkanes

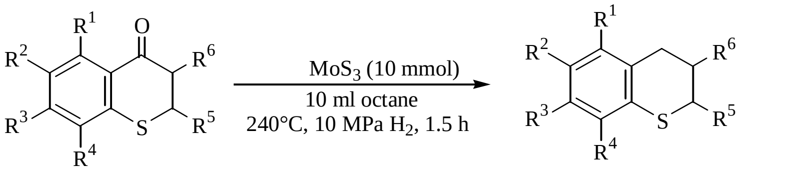
without lowering seriously the rate of hydrogenation of alkynes. The Lindlar catalyst, one of the most effective catalyst system for this selective hydrogenation, uses a combination of two catalyst poisons: lead acetate and quinoline (see Sections 1.5.2 and 4.1). It is noted that the Lindlar catalyst should be used in aprotic solvents since its effectiveness may be reduced in hydroxylic solvents.[20]

Sulfur compounds with unshielded electron pairs are all strong poisons for metallic catalysts in hydrogenation of almost all types of substrate. Horner et al. studied the effects of various poisonous compounds in the hydrogenation of cyclohexene over nickel catalyst in methanol.[21] Thiols, sulfides, thiocyanates, thioureas, thioacids, thiophenols, thiophene, and thiolane and similar cyclic thioethers were all shown to be highly poisonous. It is of interest that thiophene was less poisonous than thiolane. Unexpectedly, dodecyl methyl sulfoxide, with an unshielded electrons pair, did not show a marked inhibitory effect, although dibenzyl sulfoxide was a mild inhibitor. It has been suggested that the inhibitory effect of dibenzyl sulfoxide might be due to the thioether formed from the sulfoxide by slow hydrogenation. Sodium benzenesulfinate was an inhibitor. Sodium sulfide was a weaker poison than sodium polysulfide. Neither diphenyl sulfone nor phenyl *p*-toluenesulfonate were inhibitors, as expected form the shielded structure or oxidized state of their sulfur atoms. Greenfield demonstrated that sodium sulfite inhibited completely the hydrogenation of *p*-nitrophenol over Pd–C after slow uptake of one-third of the amount of hydrogen required for completion.[3] According to Maxted, the toxicity of sulfite ion relative to hydrogen sulfide is 0.63.[2] The poisoning by sulfur compounds has been utilized in the Rosenmund reduction of acid chlorides to aldehydes. Overhydrogenation of the aldehydes produced from acid chlorides has been effectively depressed by poisoning the catalyst, usually Pd–$BaSO_4$, with a sulfur-containing material such as quinoline-*S*, thioquinanthrene, phenylisothiocyanate, or thiourea (Section 13.4.6). Addition of bis(2-hydroxyethyl)sulfide to platinum catalyst has been shown to be as effective as sulfided platinum catalysts for the hydrogenation of halonitrobenzenes to haloanilines without dehalogenation (Section 9.3.2).

The sulfur compounds contained as impurities in a substrate or solvent may have a profound effect on hydrogenation, particularly over platinum metals where the amounts of catalyst used are usually much smaller than in the case of base metals. An excellent way to remove such impurities is to treat the sample with Raney Ni at slightly elevated temperatures[22] (usually 50–80°C). The impurities in benzene or cyclohexane can thus be removed simply by refluxing with Raney Ni for ~0.5 h (see Section 13.3). Granatelli applied this desulfurization with Raney Ni to determine quantitatively as little as 0.1 ppm of sulfur contained in 50 g of nonolefinic hydrocarbons.[23]

The transition metal sulfide catalysts are known to be resistant to poisoning by sulfur-containing compounds. Rhenium heptasulfide (Re_2S_7)[24] and heptaselenide (Re_2Se_7)[25] have a lower tendency to cause hydrogenolysis of carbon–sulfur bonds than do the base metal sulfides. Thus, allyl phenyl sulfide was hydrogenated quantitatively to phenyl propyl sulfide over Re_2S_7 in ethanol at 150–160°C and 13 MPa H_2 and over Re_2Se_7 at 195°C and 29.2 MPa H_2. Thiophene was hydrogenated to give thio-

lane without ring opening over Re_2S_7 at 245°C and 13.6 MPa H_2 and over Re_2Se_7 at 250°C and 32.2 MPa H_2 (see eq. 13.98). Hydrogenation of sulfur-containing unsaturated compounds has also been achieved over palladium catalysts. Thiophene and substituted thiophenes,[26] dihydrothiophenes,[27] and 5,6-dihydro-2*H*- and -4*H*-thiopyrans[27] were converted to the corresponding saturated compounds over Pd–C under mild conditions, although large amounts of catalysts have usually been employed. Successful hydrogenolysis of dihydrobenzothiopyranones to the corresponding dihydrothiopyrans was achieved over molybdenum(VI) sulfide (MoS_3) as catalyst at 240°C and 10 MPa H_2 (eq. 2.2).[28] The hydrogenation of 2,3-dihydro-1*H*-naphtho[2,1-*b*]thiopyran-1-one (**2**, R^1, R^2 = benz; $R^3 = R^4 = R^5 = R^6$ = H) over MoS_3 under the same conditions gave a 96% yield of the corresponding dihydrothiopyran while over 5% Pd–C and 5% PdS–C the yields were only 18 and 51%, respectively.



(2.2)

2
(5 mmol)

95%
($R^1 = R^2 = R^3 = R^4 = R^5 = R^6$ = H)

The poisoning by oxygen functions is not always observed and depends largely on the nature of catalysts as well as on the structure of the oxygen compounds. Oxidized products contained in olefins and ethers may have inhibitory effects on platinum metal catalysts, particularly on hydrogenations over rhodium, palladium, and platinum. To obtain reproducible results, careful purification of olefins by distillation and/or passage through a column of alumina or silica has been recommended.[29] Hydrogenation of unpurified methyl linolenate over palladium catalysts is often selectively hydrogenated to methyl octadecenoates, with practically no further hydrogenation to methyl stearate.[30] Ethers usually contain inhibitors resulting from oxidized products and must be purified before used as a solvent for hydrogenations over the platinum metals except ruthenium. Tetrahydrofuran can be purified conveniently by drying and then distilling from lithium aluminum hydride, or by treating with a ruthenium catalyst and hydrogen until no more hydrogen has been absorbed, followed by distillation over sodium.[10]

Direct addition of methanol or ethanol to the platinum metal catalysts that have been stored in air may result in fire or partial loss of their catalytic activity due to formation of inhibitors (see, e.g., Tables 5.5 and 13.6). Freshly prepared Raney Ni, when stored under ethanol, not only loses gradually its high activity, but also its nature may be modified probably by the carbon monoxide abstracted from the ethanol (see Section 3.7.2). Acetic acid and other organic acids may contain substances that have inhibitory effects on hydrogenations over platinum metals. Purification of acetic acid by boiling with potassium permanganate, as usually recommended, and a simple distillation[31] has been found to be insufficient for use as the solvent in the hydrogenation of aromatic compounds over platinum and rhodium catalysts. Reproducible results

were obtained only by using acetic acid that had been purified by a careful and efficient fractional distillation.[32] The benzoic acid prepared by air oxidation of toluene contains small amounts of various compounds harmful to the catalytic activity of platinum metal catalysts, and may be purified best by sublimation, or by treatment with Pd–C at 100–200°C under a high hydrogen pressure in a solvent for hydrogenation or with 0.2–10% (for benzoic acid) of concentrated sulfuric acid, followed by neutralization and distillation (see Section 11.4).

2.2.2 Temperature and Hydrogen Pressure

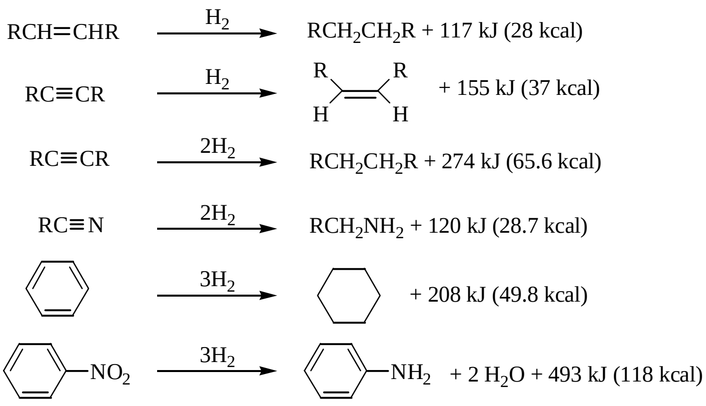
Use of elevated temperatures and pressures is usually favorable for increasing the rates of hydrogenation and hence shortening the reaction time. The amounts of catalyst to be used may also be reduced under these conditions, unless the catalyst is deactivated, as is often the case with unsupported platinum metals. Hydrogenations that proceed only slowly or not at all at a low temperature may be achieved successfully merely by raising the temperature (and also the pressure), as is usual in the hydrogenation of aromatic rings over nickel catalysts. In many cases the hydrogenation of aromatic and heterocyclic[33] compounds has been carried out successfully using palladium catalysts at elevated temperatures (see, e.g., eqs. 11.24 and 11.54). Sterically hindered unsaturated compounds may also become susceptible to hydrogenation at an elevated temperature. The inhibitory effect of catalyst poisons may sometimes be overcome merely by raising the reaction temperature.

On the other hand, hydrogenations under mild conditions, in particular those at ordinary temperature and pressure, are advantageous for monitoring the extent of conversion of substrate exactly and thus achieving selective hydrogenation successfully, as in selective hydrogenation of alkynes to alkenes and in selective hydrogenation of the carbon–carbon double bond of unsaturated carbonyl compounds.

For rapid hydrogenations, care must be taken to ensure that the reaction does not proceed too violently, particularly in a large-scale hydrogenation. This can be done by adjusting the amount of catalyst and the reaction temperature, since hydrogenations are usually highly exothermic, as seen from the heats of hydrogenation given in Scheme 2.1. A hydrogenation started at room temperature often causes a considerable rise in temperature during hydrogenation and an increase in the rate, which may sometimes result in catalyst deactivation or lower selectivity, although the rise in temperature often favors the hydrogenation to be carried to completion within a short time. Therefore hydrogenations that are reportedly carried out "at room temperature" have frequently been performed at a higher temperature unless an efficient system for regulating the temperature has been available.

The effect of hydrogen pressure on the rate of hydrogenation may depend on various factors such as the catalyst, the substrate, the reaction conditions, and others. In most hydrogenations, however, increasing the hydrogen pressure is undoubtedly favorable for increasing the rate, reducing the reaction time, and an efficient use of catalyst.

Adkins et al. studied the rate of hydrogenation of acetoacetic ester, dehydroacetic acid, benzene, phenol, and aniline over Ni–kieselguhr at pressures from 2.7 to 35 MPa



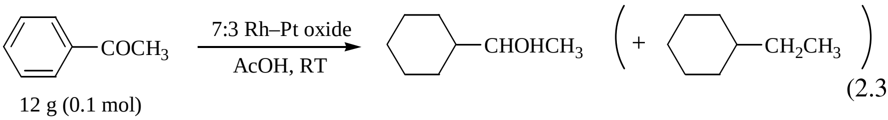
Scheme 2.1 Approximate heats of hydrogenation of representative unsaturated organic compounds.

H_2.[34] A considerable difference with respect to the effectiveness of increased hydrogen pressure in increasing the rate has been observed between the compounds. The hydrogenation of phenol and benzene (at 120°C) was relatively insensitive to increases in pressure: it proceeded well in the 3–4-MPa range, increased with pressure up to the 15–17-MPa range (~50–70% increase), but was not sensitive to further increase in pressure up to 33 MPa. Hydrogenation of acetoacetic ester (at 150°C) was considerably more sensitive to the increase in hydrogen pressure. The rate of hydrogenation of aniline (in methylcyclohexane at 175°C) was 3–4 times as great at 19 MPa as at 3.4 MPa. However, increasing the pressure in the higher ranges up to 35 MPa was not found to be particularly advantageous. The effect of pressure on the rate of hydrogenation of dehydroacetic acid to 4-heptanone was even greater; the rate at 14.9 MPa was twice, and that at 32.3 MPa 4 times, as great as that at 10.8 MPa.

Application of high pressures is in most cases indispensable for performing the hydrogenations over copper–chromium oxide catalysts in reasonable rates. Adkins and Connor observed that at an average pressure of 3.5 MPa H_2 the hydrogenation of 1.73 mol of acetone over 1 g of copper–chromium oxide at 150°C proceeded to the extent of only 17% in 0.5 h, while at a pressure of 14.8 MPa H_2 60% of acetone was hydrogenated and the hydrogenation was 95% complete at 21.2 MPa H_2. At the end of 1 h the percentage of hydrogenation was 22, 92, and 100% for the three pressures given above.[35]

Hydrogenations over the platinum metals, particularly over platinum, palladium, and rhodium catalysts, have been performed very often at atmospheric or low pressures below ~0.4 MPa. This probably stems from the fact that such low-pressure hydrogenations can be conveniently carried out in a glass reaction flask or bottle and these platinum metals are sufficiently active under such low-pressure conditions. However, application of high pressures of hydrogen may also be beneficial for platinum metals, as for the base metals, to complete a hydrogenation in a shorter time. Baker and Schuetz have shown that under high hydrogen pressure, simple benzenoid

hydrocarbons may be hydrogenated on a preparative scale within a practical period of time over Adams platinum oxide in acetic acid at room temperature.[36] As an example, 21 g (0.23 mol) of toluene was completely hydrogenated within 20 min at 13.8 MPa H_2 over 0.67 g of platinum oxide in 25 ml of acetic acid at 25°C. Benzene and *m*-xylene were hydrogenated even more rapidly, and the hydrogenations of phenol, *o*-cresol, and 2-naphthol were only slightly slower. Apparently, the first-order kinetics in hydrogen pressure was found to hold in the range of 6.9–14.3 MPa for benzene, or 0.0226 mol of benzene was hydrogenated in 12 min at 14.3 MPa H_2, compared to 41 min at 6.9 MPa H_2, over 0.063 g of platinum oxide in 4 ml of acetic acid at 26°C. Application of high hydrogen pressures has also been found to be very effective for the hydrogenation of various aromatic compounds over 7:3 rhodium–platinum oxide catalyst.[37] As an example, 7.21 g (0.1 mol) of benzene was hydrogenated completely in 5 min at 12.9–9.7 MPa H_2 over 0.05 g of prereduced 7:3 rhodium–platinum oxide in 50 ml of acetic acid at 24°C. In the presence of a substrate to be hydrogenated the reduction of the rhodium–platinum oxide to the metal requires 10–20 min, depending on the substrate, at room temperature and 9.8 MPa H_2, and then rapid absorption of hydrogen takes place. Equation 2.3 compares the hydrogenation of acetophenone at atmospheric pressure with that at 14.7–11.3 MPa H_2.[38] If we express the relative efficiency in the use of catalyst in a hydrogenation in terms of the reversal of (reaction time × amount of catalyst), the relative efficiency in the hydrogenation of acetophenone over 7:3 rhodium–platinum at 14.7–11.3 MPa H_2 to that at atmospheric pressure is given by $(0.20 \times 3.5)/(0.05 \times 0.58) = 24$. Thus, acetophenone is hydrogenated 24 times as effectively at the high pressure as at atmospheric pressure. It is also noted that the hydrogenation at high pressure gives a greater yield of 1-cyclohexylethanol than at atmospheric pressure, indicating a lesser amount of hydrogenolysis to give ethylcyclohexane at high pressure. Similarly, the rate of hydrogenation of aniline over the rhodium–platinum catalyst in acetic acid was about 30 times as great at 14.6 MPa H_2 as at atmospheric pressure.[15]



(2.3)

H_2 pressure (MPa)	Amount of catalyst (g)	Reaction time (h)	Yield of saturated alcohol (%)
0.1	0.20	3.5	80
14.7–11.3	0.05	0.58	86

In some hydrogenations, however, the rate of hydrogenation has been found to be independent of hydrogen pressure. Smith and Bedoit, Jr. have found that the hydrogenations of aliphatic nitro compounds over Adams platinum in acetic acid are zero order in hydrogen pressure and first-order in the concentration of the nitro compounds, as studied in the pressure range of 0.1–0.5 MPa, while for aromatic nitro compounds the hydrogenations are first order in hydrogen pressure and zero order in the concentration of the substrates.[39] Higashijima and Nishimura observed that the rate of hydrogenation of *p*-cresol over 5% Pd–C in cyclohexane (or methylcyclohexane) at 80°C was almost

independent of hydrogen pressure in a wide range of 0.15–8.0 MPa.[40] The rate over Pd–C A (Section 1.5.2) increased with increasing hydrogen pressure from 0.15 to 1.0 MPa, but further increase of hydrogen pressure to 8.0 MPa had only a slight effect on increasing the rate. On the other hand, the rate of hydrogenation of the intermediate 4-methylcyclohexanone to the alcohol always increased much more definitely than in the case of *p*-cresol. In line with these kinetics for hydrogen pressure, the relative reactivity of the ketone to cresol over Pd–C increased from 0.047 at 0.15 MPa H_2 to 0.62 at 8.0 MPa H_2, and the maximum yields of the ketones in the course of the hydrogenation were greater (86–88%) at low hydrogen pressure (0.15 MPa) than at high pressures (40–60%) (see Section 11.2.2). In many other cases the selectivity of hydrogenation is a function of hydrogen pressure.[38,41] Siegel and Smith found a marked effect of hydrogen pressure on the stereochemistry of hydrogenation of 1,2-dimethylcyclohexene over Adams Pt in acetic acid at 25°C.[42] The *cis/trans* ratio of the 1,2-dimethylcyclohexane formed increased from 4.5 at 0.1 MPa H_2 to 21 at 30 MPa H_2. The effects of hydrogen pressure were quite different for 2-methyl-1-methylenecyclohexane and 1,6-dimethylcyclohexene, where the *cis*/*trans* isomer ratio of the 1,2-dimethylcyclohexane formed was almost independent of hydrogen pressure or slightly decreased with increasing hydrogen pressure.

Examples for various practical hydrogenations can be seen in a large number of equations in Chapters 3–13 with experimental details. An appropriate catalyst, the ratio of catalyst to substrate, the temperature, the hydrogen pressure, the solvent, the additive, if necessary, and the reaction time are usually given in these equations, which should be helpful for a choice of optimum conditions for performing a hydrogenation successfully.

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CHAPTER 3

Hydrogenation of Alkenes

The carbon–carbon double bond is in general among the functional groups that are most readily hydrogenated, unless highly substituted and/or strongly hindered. Although the discovery of Sabatier and Senderens in 1897 that ethylene reacted with hydrogen over reduced nickel oxide to give ethane was made at a high temperature in the vapor phase,[1] a large number of alkenes have later been hydrogenated successfully in the liquid phase, frequently under mild conditions using platinum, palladium, and active nickel catalysts such as Raney Ni. However, application of elevated temperatures and/or pressures is preferred in larger-scale hydrogenations to complete the reaction within a reasonable time using relatively small amounts of catalyst. It is usual that industrial processes, such as the hydrogenation of glyceride oils,[2] are carried out at considerably higher temperatures than required for a small-scale hydrogenation in the laboratory. High temperatures and pressures are also required for hydrogenations over such catalysts as copper–chromium oxide and other transition metal oxides and sulfides.

The hydrogenation of mono- and disubstituted double bonds is usually rather rapid over most catalysts even under mild conditions. The heat of hydrogenation is also greater for mono- and disubstituted ethylenes than for tri- and tetrasubstituted ones, as shown in Scheme 3.1.[3] Accordingly, care must be taken to prevent the reaction from proceeding too violently with less hindered olefins; this can be achieved by adjusting the reaction temperature and the amount of catalyst. For obtaining reproducible results, careful purification of olefins, such as by distillation and/or passage through a column of alumina or silica,[4] is recommended.

$$CH_2{=}CH_2 + H_2 \longrightarrow CH_3CH_3 + 32.8\ \text{kcal (137 kJ)}$$

$$CH_3CH{=}CH_2 + H_2 \longrightarrow CH_3CH_2CH_3 + 30.1\ \text{kcal (126 kJ)}$$

$$CH_3CH{=}CHCH_3\ (\textit{cis}) + H_2 \longrightarrow CH_3CH_2CH_2CH_3 + 28.6\ \text{kcal (120 kJ)}$$

$$CH_3CH{=}CHCH_3\ (\textit{trans}) + H_2 \longrightarrow CH_3CH_2CH_2CH_3 + 27.6\ \text{kcal (116 kJ)}$$

$$(CH_3)_2C{=}CHCH_3 + H_2 \longrightarrow (CH_3)_2CHCH_2CH_3 + 26.9\ \text{kcal (113 kJ)}$$

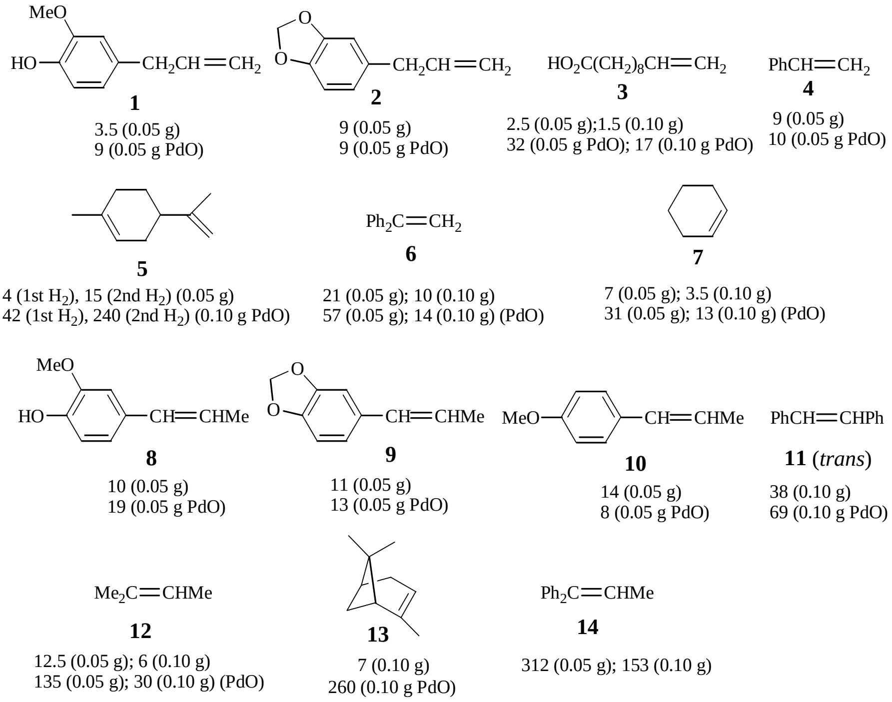
$$(CH_3)_2C{=}C(CH_3)_2 + H_2 \longrightarrow (CH_3)_2CHCH(CH_3)_2 + 26.6\ \text{kcal (111 kJ)}$$

Scheme 3.1 Heats of hydrogenation of ethylene and methyl-substituted ethylenes (82°C).

3.1 ISOLATED DOUBLE BONDS: GENERAL ASPECTS

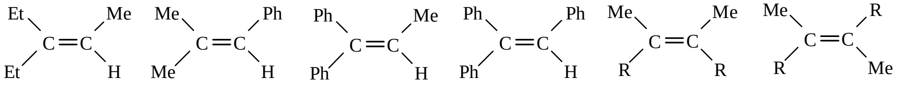
In general, the ease of hydrogenation of an isolated double bond depends primarily on the degree of substitution with respect of the double-bond carbons; the ethylenes substituted to a lesser extent are hydrogenated faster than are more highly substituted ones, and tetrasubstituted ethylenes are hydrogenated at the slowest rates. The nature and the size and degree of branching of the substituents are also important factors, the effects of which, however, may vary with catalyst, solvent, and impurity or additive.

Kern et al. studied the effect of substituents on the rate of hydrogenation over Adams platinum and palladium oxides in ethanol.[5] It is seen from the results summarized in Scheme 3.2 that, over platinum oxide, monosubstituted olefins (**1**–**4**) are hydrogenated most rapidly but a second substitution has little effect on the rate when unsymmetrically located, that is, one of the double bond carbons having two hydrogens (**5**, the side chain, and **6**), although **6** with two phenyl groups is hydrogenated more slowly than **5**. With the symmetrically disubstituted olefins, the rate of hydrogenation depended considerably on the character of the substituents. Dialkyl (**7**) or a methyl and an aryl substitutions (**8**–**10**) had only a slight effect on the rate, while a pro-



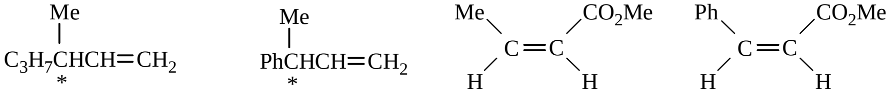
Scheme 3.2 Time (in minutes) for the uptake of 1 molar equivalent of H_2 in the hydrogenation of substituted ethylenes (0.1 mol) over Adams platinum oxide (or palladium oxide) (the amount in parentheses) in 150 ml 95% ethanol at 25°C and 0.2–0.3 MPa H_2.

nounced slowing up of the hydrogenation was observed when two phenyl groups were present (**11**). With the trisubstituted olefins, trimethylethylene (**12**), α-pinene (**13**) and the second double bond in limonene (**5**) were hydrogenated rapidly, whereas diphenylmethylethylene (**14**) was hydrogenated definitely more slowly. Over palladium oxide, it is noteworthy that the trialkyl-substituted double bonds in **5**, **12**, and **13** are hydrogenated much more slowly than the disubstituted ethylenes other than **5** and **11**. Rather slow uptake of the first mole of hydrogen in **5** might be due to extensive isomerization of the disubstituted to the tetrasubstituted double bond. Similar effects of substituents were also obtained by Lebedev et al. with platinum black (Willstätter) in ethanol at atmospheric temperature and pressure.[6,7] In most cases the rates of hydrogenation over platinum remained fairly constant until hydrogen nearly equivalent to the olefin had been absorbed,[6,8] indicating the zero-order kinetics with respect to the concentration of substrate.



I **II** **III** **IV** **V** **VI**

Different effects on the rate were observed over palladium catalysts with respect to the phenyl group substitution. Thus, Kazanskii et al. obtained the following order in the rate of hydrogenation of trisubstituted olefins **I**–**IV**: **III** > **II** > **IV** > **I** over palladium, in contrast to the order: **I** > **II** > **III** > **IV** over platinum.[9] In the hydrogenation of binary mixtures of **I** with **II**, **III**, or **IV** over palladium, the phenyl-substituted ethylenes were selectively hydrogenated. Raney Ni behaved similarly to palladium. The rate of hydrogenation was the greatest with **III**, which was hydrogenated as fast as on palladium and much faster than on platinum. Similarly, the rate for **IV** over nickel, which was as great as for **II** and much lower than for **III**, was greater than on platinum, but smaller than on palladium. As on palladium, the most slowly hydrogenated compounds were the aliphatic derivatives **I** and trimethylethylene.[10] Tetraphenylethylene, which was not reduced over platinum at room temperature and pressure, was hydrogenated slowly in the presence of palladium.[11] A similar effect of the phenyl group over palladium was also observed in the stereochemistry of hydrogenation of tetrasubstituted ethylenes **V** and **VI**. When R was phenyl, 1,2-*cis* addition occurred almost exclusively over palladium,[12,13] but when R was carboxyl, 1,2-*cis* addition decreased to 86 and 70% with **V** and **VI**, respectively,[12] and with 1,2-dimethylcyclohexene (**V**: R = $-(CH_2)_4-$)[14] and $\Delta^{9,10}$-octalin,[15] apparent 1,2-*trans* addition predominated. The characteristic effect of the phenyl group in palladium catalyzed hydrogenation has also been observed in a marked decrease in racemization from 60% with an alkyl-substituted ethylene **15** to 10% with α-phenethyl-substituted ethylene **16**, where racemization is expected to occur via isomerization to a phenyl-substituted ethylene.[16] Similarly, in the deuteration of phenyl-substituted unsaturated compounds over palladium, the deuterium distributions in saturated products were more symmetrical and dideuterio species were more prevalent.[17] Further, it was observed that methyl *cis*-2-butenoate (methyl isocrotonate) (**17**) readily isomerized to the *trans* isomer during hydrogenation, while methyl *cis*-cinnamate (**18**) did not isomerize to the *trans* isomer over Pd–C.[17]



15 **16** **17** **18**

Brown et al.[18,19] and Brunet et al.[20] studied the rates of hydrogenation of various olefinic compounds over P-1 and P-2 nickel borides and over a nickel catalyst designated Nic, obtained from NaH–*t*-PeONa–Ni(OAc)$_2$, respectively, in ethanol at 25°C and 1 atm H_2 (Table 3.1). Over P-1 Ni, the decrease in the rate of hydrogenation with 2-methyl-1-

TABLE 3.1 Rates of Hydrogenation of Alkenes over P-1 and P-2 Nickel Boride and Nic Catalysts

Compound	P-1 Ni[a] Initial Rate[d]	P-1 Ni[a] Relative Rate	P-2 Ni[b] Initial Rate[d]	P-2 Ni[b] Relative Rate	Nic[c] Initial Rate[d]	Nic[c] Relative Rate
1-Octene	72	1.0	119	1.0	34	1.0
3-Methyl-1-butene	45	0.63	44.8	0.38	—	—
3,3-Dimethyl-1-butene	56	0.78	11.9	.10	—	—
2-Methyl-1-butene	36	0.50	—	—	—	—
2-Methyl-1-pentene	—	—	2.9	0.025	—	—
2-Methyl-1-hexene	—	—	—	—	9.5	0.28
cis-2-Pentene	—	—	6.9	0.058	—	—
trans-2-Pentene	—	—	1.8*	0.015	—	—
cis-2-Hexene	—	—	—	—	12	0.35
trans-2-Hexene	—	—	—	—	12	0.35
2-Methyl-2-butene	7	0.10	—	—	—	—
2-Methyl-2-pentene	—	—	0.22*	0.002	—	—
2-Methyl-2-hexene	—	—	—	—	0.5	0.015
2,3-Dimethyl-2-butene	2	0.03	0	0	—	—
Cyclopentene	56	0.78	13.4	0.11	23	0.68
Cyclohexene	31	0.43	1.8*	0.015	10	0.29
1-Methylcyclohexene	—	—	—	—	0.15	0.0044
Cycloheptene	—	—	47	0.40	22	0.65
Cyclooctene	43	0.60	15	0.13	3	0.09
Cyclododecene	—	—	—	—	2.8	0.082
Norbornene	80	1.1	125	1.06	33	0.97
Styrene	63	0.88	—	—	44	1.3
α-Methylstyrene	49	0.68	5.6	0.047	28.5	0.84

[a]Data of Brown, C. A. *J. Org. Chem.* **1970**, *35*, 1900. Reprinted with permission from American Chemical Society. The substrate (40 mmol) was hydrogenated over 5.0 mmol of catalyst (0.29 g Ni) in 50 ml 95% ethanolic solution at 25°C and 1 atm H_2.

[b]Data of Brown, C. A.; Ahuja, V. K. *J. Org. Chem.* **1973**, *38*, 2226. Reprinted with permission from American Chemical Society. The reaction conditions were the same as for P-1 Ni.

[c]Data of Brunet, J.-J.; Gallois, P.; Caubere, P. *J. Org. Chem.* **1980**, *45*, 1937. Reprinted with permission from American Chemical Society. The substrate (10 mmol) was hydrogenated over 0.5 mmol of catalyst (0.029 g Ni), obtained from *t*-PeOH as activating agent, in 15 ml ethanol at 25°C and 1 atm H_2.

[d]Average rate from 0 to 20% reaction in ml H_2 at STP·min–1 (* values measured between 0 to 5 or 10% hydrogenation).

butene, an unsymmetrically disubstituted ethylene, is not significant, compared to 1-octene, but significantly marked with 2-methyl-2-butene, a trisubstituted ethylene. In contrast, over P-2 Ni the corresponding di- and trisubstituted ethylenes, 2-methyl-1-pentene and 2-methyl-2-pentene, were hydrogenated in the relative rates of only 0.025 and 0.002, respectively, compared to 1-octene. Over P-1 Ni 2,3-dimethyl-2-butene, a tetrasubstituted ethylene, was hydrogenated, although very slowly, but over P-2 Ni it did not react at all. Thus, the hydrogenation over P-2 Ni was found to be markedly more sensitive to the alkyl substitution, compared to the hydrogenation over platinum, Pt–C, and P-1 Ni. The order in the reactivity of cycloalkenes was $C_5 > C_8 > C_6$ over P-1 Ni and $C_7 > C_8 \geq C_5 > C_6$ over P-2 Ni. The differences in the rate between the cycloalkenes were also much greater over P-2 Ni than over P-1 Ni. It is noteworthy that norbornene was hydrogenated more rapidly than any other cycloalkenes and even more rapidly than 1-octene over both P-1 and P-2 nickel borides. It is also of interest to note that over P-1 Ni the zero-order kinetics in concentration of substrate apparently holds for the hydrogenation of 1-hexene, 2-methyl-1-butene, and cyclopentene while over P-2 Ni only the hydrogenation of norbornene is zero-order, and with the other alkenes, especially even with 1-octene and cyclopentene, the rates tend to decrease with conversion. The effects of substituents on the rates over Nic appear to be similar to those over P-1 Ni rather than over P-2 Ni. Cyclohexene, however, was more reactive than cyclooctene over Nic, in contrast to the results over P-1 and P-2 catalysts.

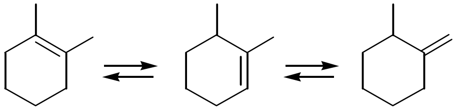
3.2 HYDROGENATION AND ISOMERIZATION

The relationship between the structure of olefins and their reactivities in hydrogenation as described above is complicated by the double-bond migration and the *cis–trans* isomerization that may accompany the hydrogenation.

In the hydrogenation of 1-butene over Pd–$BaSO_4$ in 95% ethanol at −8°C and one atmosphere pressure, the residual butenes were 8% 1-butene and 92% 2-butene at 20% hydrogenation.[21] *Cis–trans* isomerization was also relatively rapid under these conditions. Similarly, over nickel wire the double bond migration of 1-butene was reported to occur 2.5 times faster than hydrogenation at about 60°C[22] and the *cis–trans* isomerization of 2-butene was 4–5 times faster than hydrogenation at 75°C.[23] The *cis* isomers are usually known to hydrogenate faster than that of the corresponding *trans* isomers. Thus, *cis*-dimethylstilbene was found to hydrogenate much faster than *trans*-dimethylstilbene over Pd–C in ether.[12] Similarly, the hydrogenation of *cis* acids or their esters has been found to proceed faster than that of the corresponding *trans* isomers over platinum and palladium catalysts.[24,25] However, Dobson et al. observed that, although the presence of *cis*-4-undecene inhibited the hydrogenation of the *trans* isomer over Pd–C, pure *trans*-4-undecene was hydrogenated much more rapidly than the *cis* isomer.[26] When the amount of catalyst was reduced to such an extent that no hydrogenation occurred, *cis*-4-undecene was transformed in one hour at room temperature into a mixture containing about 70% of the *trans* isomer.

The hydrogenation of 1,2- (**19**) and 1,6-dimethylcyclohexene (**20**) and 2-methylmethylenecyclohexane (**21**) over Pd–Al_2O_3 at 25°C and 1 atm H_2 gave almost the

same isomer mixture at about 60% completion due to extensive isomerization, and the saturated product of nearly the same *cis/trans* isomer ratio was obtained with any of the three isomers as the starting material.[14]



19 **20** **21**

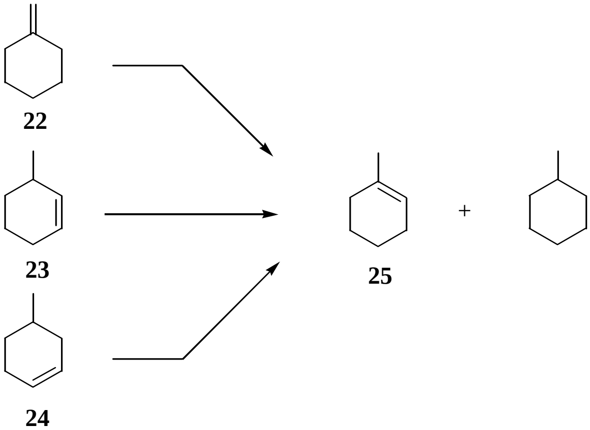
It has been recognized that usually the isomerization of olefins as well as the exchange reaction with deuterium are depressed in the absence of hydrogen (or deuterium) but greatly promoted in the presence of hydrogen.[23,26,27] The extent of olefin isomerization depends primarily on the nature of catalyst metal. However, the impurities or additives as well as the reaction conditions may also become factors affecting the isomerization.

It is often encountered that characteristic selectivity of a catalyst metal in a hydrogenation reaction is closely related with its tendency toward the double-bond isomerization. For example, the high selectivity of palladium in the partial hydrogenation of alkynes[28] or the predominant formation of stable isomers in the hydrogenation of isomeric dimethylcyclohexenes over palladium[14] are considered to result from an unusually high activity of palladium for olefin isomerization. Bond et al. studied the hydrogenation and isomerization of 1-butene in vapor phase over alumina-supported transition metals and found that the tendency of catalyst metals toward isomerization (the ratio 2-butene/butane at initial stage) decreased in the following order: Co > Ni ≅ Rh (≥ 80°C) > Pd > Ru > Os > Pt ≅ Cu.[28,29] From these and other results, it has been pointed out that the first-row metals (Fe, Co, Ni) and the second-row metals (Ru, Rh, Pd) of group VIII (or groups 8–10) in the periodic table show greater tendency for isomerization and exchange than the third-row metals (Os, Ir, Pt).[28–30] In the liquid phase, however, palladium has been known to be more active for olefin isomerization than any of the other group VIII metals. Gostunskaya et al. obtained the following order of metals in the isomerization to hydrogenation ratio (given in parentheses) of 1-hexene in ethanol at 40°C and 1 atm H_2: Pd (1.7) > Ni (1.45) > Rh (0.49) ≥ Ru (0.41) >> Os (0.19) > Pt (0.12) ≥ Ir (0.10).[31] In the hydrogenation of 1-octene over unsupported metals in isopropyl alcohol at 25°C and 1 atm H_2, the order was Pd (2.05) >> Rh (0.125) ≥ Ru (0.12) >> Pt (0.025) ≅ Ir (0.025) > Os (0.009).[32] In the hydrogenation of 1-octene with various nickel catalysts in cyclohexane (25°C, 1 atm H_2), the ratio decreased in the following order: T-4 Raney Ni[33] (1.66) > W-7 Raney Ni (1.11) > U-Ni-B[34] (0.44) > U-Ni-A[35] (0.23) > T-4 Raney Ni treated with 1-hexene (0.17) > Ni (NRIM)[36] (0.13) > reduced Ni (0.093).[37] Thus, the isomerization to hydrogenation ratio is much greater over active Raney Ni with a large amount of adsorbed hydrogen such as T-4 and W-7 than over the other nickel catalysts or over the T-4 Raney Ni that was treated with 1-hexene under an atmosphere of argon to remove adsorbed hydrogen. Similarly, with cobalt catalysts the following order was obtained: W-7 Raney Co (1.16) > U-Co-A[38] (0.35) > U-Co-B[38] (0.26) > reduced Co (0.063).[37] Brown and

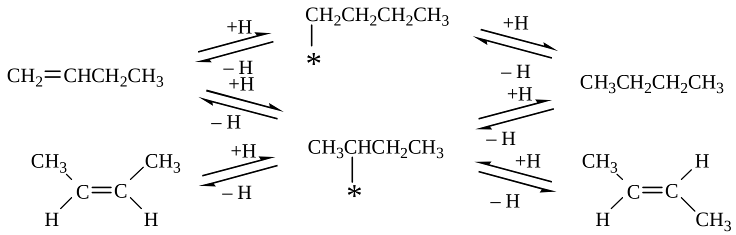
Brown found a great difference in isomerizing tendency between P-1 and P-2 nickel boride catalysts.[39,40] After absorption of 0.5 mol of H_2 in ethanol at 25°C and 1 atm H_2, 1-pentene yielded the reaction mixture containing only 2 mol% (isomerization to hydrogenation ratio = 0.039) of 2-pentene (*cis/trans* = 7) with P-2 Ni, while P-1 Ni and, in particular, Raney Ni gave the products containing substantially more 2-pentene (7 and 23 mol%; isomerization:hydrogenation ratio 0.14 and 0.45, respectively). Over Nic catalyst with 1-octene, 3% 2-octenes were found at 50% hydrogenation and 6% at 90% hydrogenation, indicating a slightly greater tendency toward isomerization than over P-2 Ni.[20]

The relative rate of isomerization to hydrogenation can be decreased by the addition of nucleophiles such as strong bases, amines, phosphines, and carbon monoxide[41] or affected by the nature of solvents.[42] Augustine et al. studied the effect of solvents on the isomerization of methylenecyclohexane (**22**) and 3- and 4-methylcyclohexenes (**23** and **24**) to 1-methylcyclohexene (**25**) over palladium, platinum, and rhodium catalysts (Scheme 3.3).[42] With the exception of the hydrogenation of **22** over palladium, the isomerization to **25** was depressed in the presence of benzene, and more favored in ethanol than in pentane, as compared by the amounts of **25** found in the reaction mixture at 25% hydrogenation. There was no correlation between the rates of hydrogenation and the extent to which the isomerization took place. The hydrogenations were faster in pentane than in ethanol and the slowest in benzene–ethanol.

It has generally been accepted that the double-bond migration and *cis–trans* isomerization that accompanies the hydrogenation occur via the common intermediate referred to as the half-hydrogenated state or a monoadsorbed alkane. Reversal of the half-hydrogenated state may lead to double-bond migration, *cis–trans* isomerization, racemization, and isotope exchange with deuterium. A typical hydrogenation and isomerization process via the half-hydrogenated state, which is referred to as the *as-*



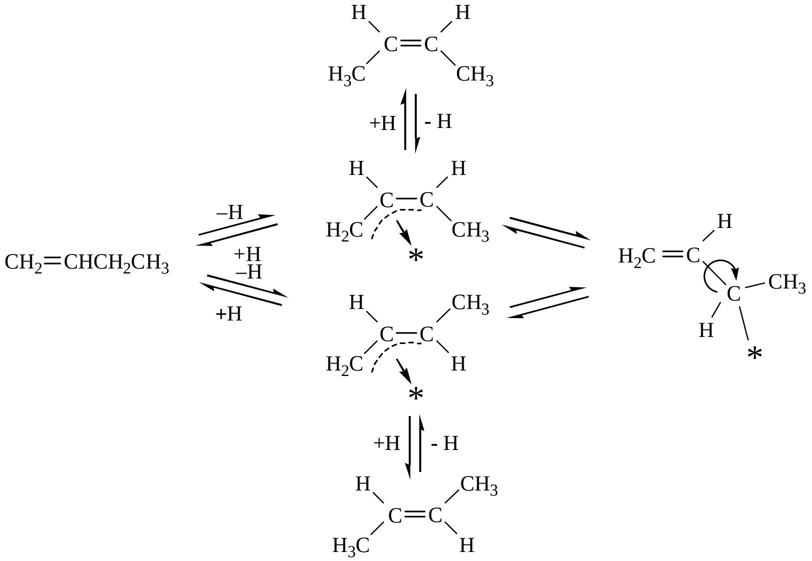
Scheme 3.3 Hydrogenation and isomerization of methylenecyclohexane and 3- and 4-methylcyclohexene.



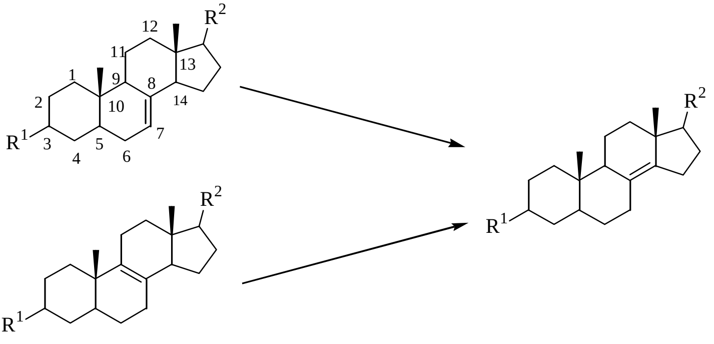
Scheme 3.4 Hydrogenation and isomerization of 1-butene via the half-hydrogenated states.

sociative mechanism or the *addition–abstraction mechanism*, is illustrated in Scheme 3.4 for the reaction of 1-butene with hydrogen.

Isomerization during hydrogenation may also occur via the π- and σ-allyl intermediates formed by abstraction of a hydrogen atom from an alkene, followed by addition of hydrogen. This process for isomerization, referred to as the *abstraction–addition mechanism*, is illustrated in Scheme 3.5 for 1-butene.[43] Isomerization via an allylic intermediate might be favored in those cases where the formation of half-hydrogenated state is strongly hindered or the surface hydrogen is rather poor and, therefore, formation of the alkyl intermediate might be slow. A typical example of the former case is the migration of Δ^7 and Δ^8 double bonds of 5α-steroids to $\Delta^{8(14)}$ position over platinum in acetic acid or palladium in ethyl acetate or acetic acid (Scheme 3.6).[44–47] The hydrogenation of these double bonds does not occur in the absence of a strong acid. In these cases, formation of the half-hydrogenated state adsorbed at the C8 carbon on the



Scheme 3.5 Isomerization of 1-butene via π- and σ-allylic intermediates.

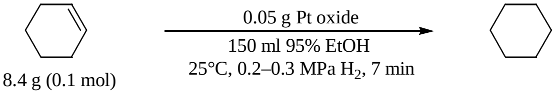


Scheme 3.6 Migration of Δ^7 and Δ^8 double bonds to $\Delta^{8(14)}$ position in 5α-steroids.

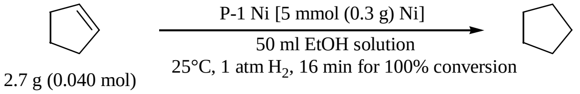
α face, which may lead to a saturated product, is prevented by the increased crowding at the β face. However, this difficulty may be avoided by the formation of the allylic intermediates through which the migration to $\Delta^{8(14)}$ is possible.[41] The formation of small amounts of *o*-xylene during the hydrogenation of 1,2-dimethylcyclohexene over palladium catalysts under ordinary conditions[14,48] may also be initiated by the abstraction of allylic hydrogens, which might occur even in the presence of hydrogen.

3.3 ALKYL-SUBSTITUTED ETHYLENES

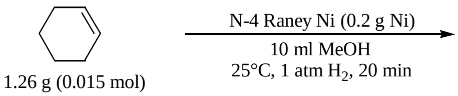
Unhindered simple olefins are usually rapidly hydrogenated under very mild conditions over platinum metal catalysts such as platinum, palladium, and rhodium as well as over active nickel catalysts such as Raney Ni, nickel boride, and Urushibara Ni. For example, 0.1 mol of cyclohexene is hydrogenated in 7 min over 0.05 g of Adams platinum oxide in ethanol at 25°C and 0.2–0.3 MPa H_2 (eq. 3.1).[5] 1-Octene and cyclopentene (eq. 3.2) are hydrogenated in rates of 11.5 and 8.6 mmol (258 and 193 ml H_2 at STP)·g Ni^{-1}·min^{-1}, respectively, over P-1 Ni in ethanol at 25°C and 1 atm H_2.[18] Hydrogenation of cyclohexene over active Raney Ni proceeds at rates of 96–100 ml H_2 at STP (4.3–4.5 mmol)·g Ni^{-1}·min^{-1} in methanol at 25°C and 1 atm H_2,[49,50] and can be completed within a short time, although usually larger catalyst: substrate ratios than required for platinum catalyzed hydrogenations are employed (eq. 3.3).[50]



(3.1)

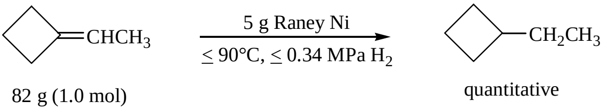


(3.2)



(3.3)

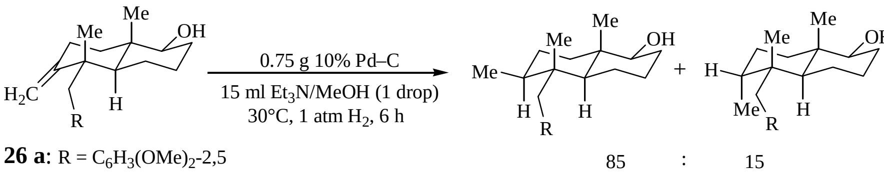
For hydrogenation of more substituted double bonds over Raney Ni, application of elevated temperature and pressure may be advantageous to complete the reaction within a reasonable time, as seen in the hydrogenation of ethylidenecyclobutane in eq. 3.4, although the reaction time was not described.[51] Hydrogenation of isopropylidenecyclobutane at 80–100°C and 0.34–0.41 MPa H_2 proceeded less readily than in the case of ethylidenecyclobutane.



(3.4)

Copper–chromium oxide catalyst is effective for the hydrogenation of alkenes at elevated temperatures and pressures. Isopropenylcyclopropane was hydrogenated to isopropylcyclopropane over barium-promoted copper–chromium oxide at 100–130°C and 10.3–13.8 MPa H_2 with little or no ring cleavage.[52] In those cases where double-bond migration may lead to more hindered isomers or racemized products, use of palladium catalysts should be avoided. Cram hydrogenated optically active 3-phenyl-1-butene in ethanol with racemization of only 1.1–2.5% over Raney Ni and 3.5% over platinum oxide whereas more extensive racemization (9.1–11.3%) occurred with 0.5% Pd–$CaCO_3$.[53] Huntsman et al. observed much more extensive racemization (32–63%) in the hydrogenation of optically active 3,7-dimethyl-1-octene and 3-methyl-1-hexene over Pd catalysts, although racemization decreased in the presence of base or at high pressure. Similar results were also obtained with (–)-3-phenyl-1-butene as substrate; over platinum oxide in acetic acid, however, racemization was only 3% with 3,7-dimethyl-1-octene.[16] The results are summarized in Table 3.2.

Hydrogenation of the exomethylene compound **26a** over an aged 10% Pd–C proved difficult because of complete isomerization of the exo double bond to the more hindered endocyclic position. However, Sarma and Chattopadhyay were successful in accomplishing the hydrogenation by using a large excess of 10% Pd–C in triethylamine containing a small amount of methanol to afford quantitatively a mixture of epimeric methyl derivatives in a ratio of 85:15 (eq. 3.5).[54] The exomethylene compound **26b** (R = Ph), however, could be hydrogenated in dry DMF or ethanol to give the product containing a mixture in a ratio of 4:1.



26 a: R = $C_6H_3(OMe)_2$-2,5
400 mg (1.16 mmol)
b: R = Ph

(3.5)

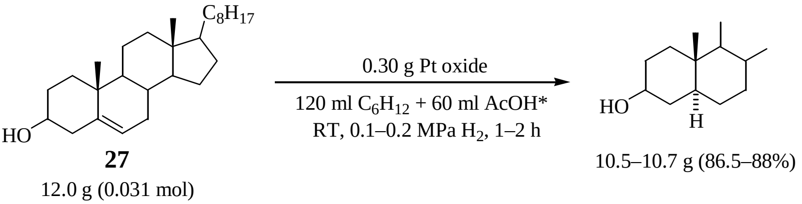
TABLE 3.2 Hydrogenation and Racemization of Optically Active Alkenes[a]

Optically active alkene	Catalyst	Solvent	Additive	% Racemization	Ref.
(–)-3-Phenyl-1-butene	0.5% Pd–$CaCO_3$	EtOH	—	9.1	53
	5% Pd–C	EtOH	—	10	16
	Raney Ni (W-2)	EtOH	—	2.5	53
	Pt oxide	EtOH	—	3.5	53
(+)-3-Methyl-1-hexene	5% Pd–C	EtOH	—	63	16
(–)-3,7-Dimethyl-1-octene	Pt oxide	AcOH	—	3	16
	5% Pd–C	EtOH	—	52	16
	5% Pd–C	—	—	52	16
	5% Pd–C	AcOH	—	57	16
	5% Pd–C[b]	EtOH	—	23	16
	0.5% Pd–$CaCO_3$	EtOH	—	47	16
	PdO	EtOH	—	41	16
	Lindlar	EtOH	—	16	16
	5% Pd–C	EtOH	KOH[c]	12	16
	5% Pd–C	EtOH	Pyridine[d]	18	16
	5% Pd–C	EtOH	Concentrated HCl	56	16

[a]Hydrogenations were carried out at room temperature and 1 atm H_2, unless otherwise noted.
[b]Hydrogen pressure, 10 MPa.
[c]Hydrogen uptake ceased at 90% saturation. The catalyst was removed and the hydrogenation completed with addition of Pt oxide and AcOH.
[d]Hydrogen uptake practically ceased at 80% saturation. The hydrogenation was completed with addition of Pt oxide and AcOH.

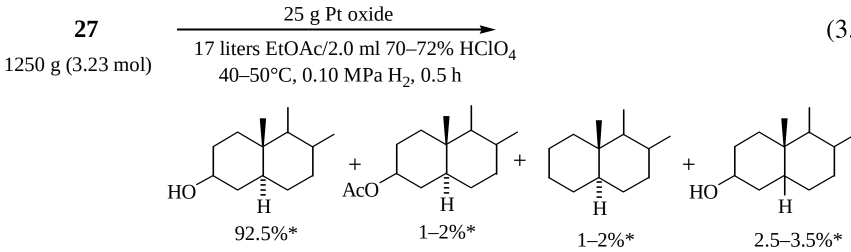
Platinum catalysts are preferred for the hydrogenation of relatively hindered olefins under mild conditions. The Δ^5 double bond in steroids, a rather hindered of trisubstituted double bonds, is usually not hydrogenated over platinum oxide in neutral medium or with Raney Ni under mild conditions. However, it may be hydrogenated without difficulty over platinum in an acidic medium. The hydrogenation of cholesterol (**27**) often experienced difficulty in proceeding to completion when performed even in acetic acid at 65–75°C.[55] The use of acetic acid as the solvent at an elevated temperature is also not advantageous because of the formation of the acetate. Nace found that the products, 5α-cholestan-3β-ol and its acetate, began to crystallize from the solution as the hydrogenation approached 75% completion, which coated the catalyst and rendered it ineffective. By employing a solvent consisting of cyclohexane and acetic acid to prevent crystallization of the products, the hydrogenation could be completed within a short time without heating the reaction mixture (eq. 3.6).[56] Hydrogenation of cholesterol as its acetate may eliminate this difficulty in solubility of the product.[57] Hershberg et al. used ethyl acetate as the solvent with addition of perchloric acid as an accelerator and obtained 5α-cholestan-3β-ol in 87–90% yield in rapid hydrogenation at an initial temperature of 40–50°C, which was then maintained by the

heat evolved.[58] Chromatographic separation of the residues after crystallization of the product indicated the presence of small amounts of 5α-cholestanyl acetate, 5β-cholestan-3β-ol, and 5α-cholestane (eq. 3.7). The formation of 5β derivative has also been observed in a more significant amount in the platinum-catalyzed hydrogenation of a Δ^5-steroid in acetic acid.[59]



(3.6)

*The solution was added to a suspension of catalyst prereduced in 30 ml AcOH.

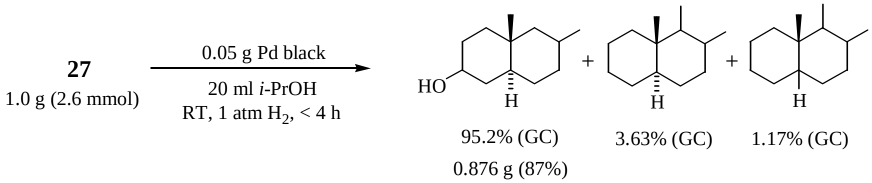


(3.7)

*The yields allowed by the results of chromatographic separation of the residues after crystallization.

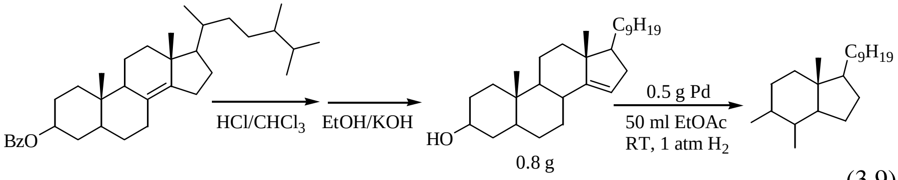
It is rather surprising that palladium catalysts have often been used successfully for the hydrogenation of Δ^5-steroids,[60] since tri- and tetraalkylsubstituted double bonds are usually hydrogenated only slowly over palladium. Augustine and Reardon, Jr. showed that the hydrogenation of cholesterol over 5% Pd–C in ethanol proceeded smoothly at room temperature and atmospheric as well as slightly elevated pressure. After one crystallization of the product from ethanol, a 90% yield of 5α-cholestan-3β-ol was obtained. Examination of the NMR (nuclear magnetic resonance) spectrum of the residue obtained from evaporation of the mother liquors indicated the presence of about 10% cholesterol (1% of the total product) with none of the 5β and hydrogenolysis products detected.[60] Nishimura et al. found that the hydrogenation of cholesterol in isopropyl alcohol over a well-washed palladium black was smoothly carried to completion at room temperature and atmospheric pressure. Isopropyl alcohol was used as the solvent, since 5α-cholestan-3β-ol was more soluble in isopropyl alcohol than in ethanol. Gas chromatographic analysis of the product showed it to consist of 95.2% of 5α-cholestan-3β-ol and 4.8% of 5α- and 5β-cholestanes with no starting cholesterol (eq. 3.8).[61] The results by Augustine and Reardon, Jr. that the reaction became sluggish after 70–80% completion and 1% of cholesterol remained unchanged even after 10 h of reaction, together with the fact that no hydrogenolysis product was detected, suggest that the 5% Pd–C used by Augustine and Reardon, Jr. was of slightly alkaline character, which might have depressed the hydrogenolysis. It is probable that the hydrogenolysis took place via isomerization to the allylic Δ^4-3β-ol, since the

cholestane formed was a mixture containing the 5β isomer in as much an amount as 25%. The unusual high reactivities of steroids in palladium-catalyzed hydrogenations have been shown to result from a strong adsorption of the steroid α face onto the catalyst, which is characteristic of palladium.[61,62]



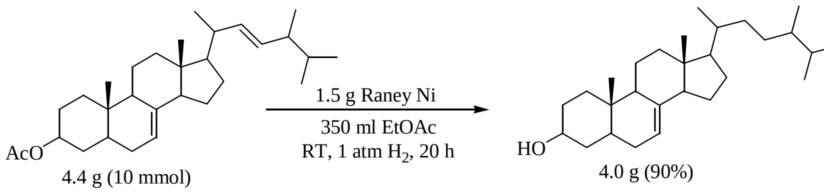
(3.8)

Isolated double bonds at the 7, 8, 9(11), and 8(14) positions in steroids (for the numbering, see Scheme 3.6) are known to be much more resistant to hydrogenation than the Δ^5 double bonds. As described in Scheme 3.6, the double bonds Δ^7 and Δ^8 are liable to migration to $\Delta^{8(14)}$ during hydrogenation over platinum oxide in acidic media or over palladium catalyst in neutral solvent without being hydrogenated. However, in the presence of dry hydrogen chloride in chloroform, $\Delta^{8(14)}$ double bond migrates to the C14 position[63–65] and can be hydrogenated to give a saturated product.[44,65] Thus, $\Delta^{8(14)}$-ergostenol (α-ergostenol) was transformed into ergostanol by prior isomerization (as benzoate) to the Δ^{14} isomer (β-ergostenol) in the presence of dry HCl in chloroform, followed by hydrogenation over palladium in ethyl acetate (eq. 3.9).[65]



(3.9)

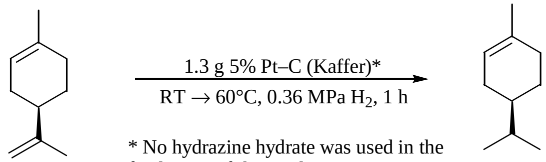
The isomerizing tendency of Δ^7 and Δ^8 double bonds is largely depressed in the hydrogenation with platinum oxide in a neutral solvent or with Raney Ni. Thus, over platinum oxide in ethyl acetate cholesta-8,24-dien-3β-ol (zymosterol) is hydrogenated selectively at the side chain to give cholest-8-en-3β-ol (zymostenol) without being accompanied by isomerization.[66] Similarly, Δ^7-ergostenol (γ-ergostenol) is obtained from ergosterol or 5,6-dihydroergosterol by hydrogenation of their acetates over platinum oxide in neutral solvent[44] or, better, over Raney Ni at room temperature and atmospheric pressure (eq. 3.10).[67]



(3.10)

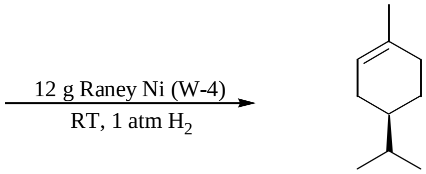
3.4 SELECTIVE HYDROGENATION OF ISOLATED DOUBLE BONDS

In general, the selective hydrogenation of compounds with two or more isolated double bonds is rather easily achieved when the degree of substitution differs between the double bonds. Equation 3.10 is an example of such cases. (*R*)-(+)-Limonene (**28**) was hydrogenated to (*R*)-(+)-carvomenthene almost quantitatively over 5% Pt–C (Kaffer)[68] (eq. 3.11)[69] or Raney Ni (eq. 3.12),[70] without use of solvent. Application of palladium catalysts to this selective hydrogenation would be unsuccessful, because extensive isomerization of the isopropenyl group to less readily hydrogenatable isopropylidene group may occur over this metal.



28 120 ml (101 g) (0.73 mol) $[\alpha]_D^{23}$ +118.7° → 121 ml (97.6%) $[\alpha]_D^{23}$ +109° (3.11)

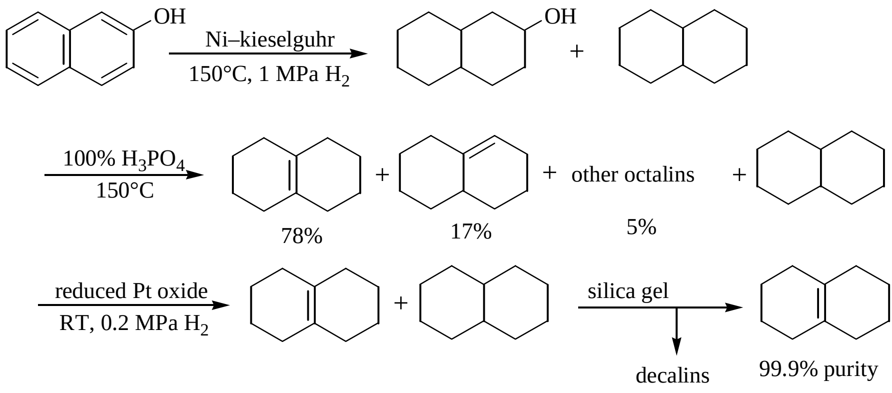
*No hydrazine hydrate was used in the final stage of the catalyst preparation.



28 190 g (1.4 mol) $[\alpha]_D^{18}$ +113° → 184 g (96%) $[\alpha]_D^{20}$ +101.8° (3.12)

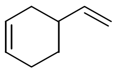
Smith and Burwell, Jr. found that $\Delta^{9,10}$-octalin, a tetrasubstituted ethylene, was not hydrogenated on Adams platinum oxide reduced in situ, probably due to the presence of alkaline substances, although it could be hydrogenated by adding acetic acid or by prereducing the catalyst in dilute acid. On the other hand, $\Delta^{1,9}$-octalin, a trisubstituted ethylene, was susceptible to hydrogenation, and $\Delta^{9,10}$-octalin of a high purity was prepared according to a reaction sequence described in Scheme 3.7, with 2-naphthol as starting material.[71]

4-Vinylcyclohexene (**29**) has been selectively hydrogenated to 4-ethylcyclohexene (**30**) in high yields of 97 and 98% over P-2 Ni[19] and Nic,[20] respectively, in ethanol at 25°C and 1 atm H_2. Both the nickel catalysts are known to be of low isomerization activity and sensitive to the structure of substrates. The same selective hydrogenation was also achieved over a nickel catalyst in the presence of ammonia, which minimized the isomerization to a more highly substituted double bond.[72] Similarly, over P-2 Ni,



Scheme 3.7 The preparation of high-purity $\Delta^{9,10}$-octalin from 2-naphthol.

5-methylenenorbornene (**31**) was readily hydrogenated to give 2-methylenenorbornane (**32**) in 96% yield. The hydrogenation of *endo*-dicyclopentadiene (**33**) has been carried out on a 3-mol (400-g) scale without difficulty to yield 5,6-dihydro-*endo*-dicyclopentadiene (**34**) in 90% distilled yield (eq. 3.13).[19]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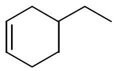
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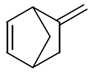
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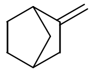
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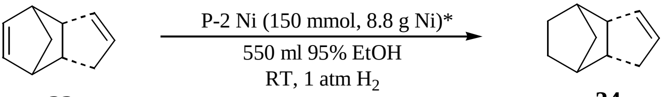


33 407 g (3.08 mol) → **34** 370 g (90%) (3.13)

*The catalyst was prepared in situ prior to the addition of substrate.

The selective hydrogenation of 1,5-cyclooctadiene (1,5-COD) and 1,5,9-cyclododecatriene (1,5,9-CDT), cyclic oligomers of 1,3-butadiene, to the corresponding monoenes has been the subject of considerable interest, since the hydrogenation may constitute one of the steps leading to the synthesis of C_8 and C_{12} lactams, dicarboxylic acids, and their derivatives.

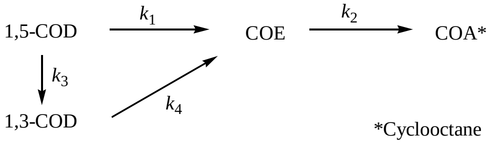
In the hydrogenation of 1,5-COD over Nic in ethanol at 25°C and 1 atm H_2, cyclooctene (COE) was obtained in a maximum yield of 93% with a ratio of the hydrogen uptake rates of 15 before and after the maximum yield.[20]

Palladium catalysts have been shown to be selective in this hydrogenation. Hanika et al. studied the hydrogenation of 1,5-COD with 0.56% Pd–γ-Al_2O_3 and two Lindlar catalysts, Pd–$CaCO_3$ (Farmakon, 5% Pd) and Pd–$CaCO_3$ (Engelhard), as catalysts in heptane at 27°C and 1 atm H_2.[73] The kinetic constants have been determined accord-

ing to the reaction pathways outlined in Scheme 3.8, assuming the respective reaction to be first-order. However, it should be understood that the rate constant k_3, defined by Hanika et al. for the isomerization of 1,5- to 1,3-COD in Scheme 3.8, is actually that for the isomerization to 1,4-COD, as it may be presumed from the fact that 1,3-COD, which is much more reactive than 1,5- and 1,4-COD, is seldom detected at all or is detected only in trace amounts during the course of the hydrogenation of 1,5-COD or even in the hydrogenation of 1,4-COD.[74,75] From the results summarized in Table 3.3, it is seen that the selectivity to COE as compared by $k_2/(k_1+ k_4)$ is higher over the Pd–Al_2O_3 than over the Lindlar catalysts. The maximum yield of COE over the Pd–Al_2O_3 is calculated to be 97.7% at 99.6% conversion.

Although the selectivity of palladium catalysts in the hydrogenation of 1,5-COD is thus very high, the results also indicate that the hydrogenation of COE to cyclooctane (COA) does not cease after the maximum yield of COE has been attained. Hirai et al. studied the hydrogenation of 1,5-COD over a colloidal palladium catalyst, prepared by reduction of palladium(II) chloride in the presence of poly(*N*-vinyl-2-pyrrolidone) in refluxing methanol with addition of sodium hydroxide, in methanol at 30°C and 1 atm H_2, and obtained a mixture consisting of 0.4% 1,5-COD, 0.3% 1,4-COD, 97.8% COE, and 1.5% COA at the uptake of 1 molar equivalent of hydrogen.[74] The initial hydrogenation rate of COE over the colloidal palladium was $\frac{1}{20}$th that of 1,5-COD. The maximum yield of COE was smaller by 2% over the catalyst prepared without adding sodium hydroxide, and the yields with this catalyst were increased by the addition of sodium hydroxide (by 0.7%) or triethylamine.

Nishimura et al. have found that 1,5-COD is hydrogenated to COE with high selectivity with palladium catalysts in the presence of small amounts of phenylacetaldehyde (PAA), among various aldehydes, with almost complete depression of further hydrogenation to COA.[76] Thus, over 5% Pd–$CaCO_3$ and palladium black in the presence of a small amount of PAA, 1,5-COD was hydrogenated to give the maximum COE yields of 97.6 and 97.4%, respectively, within 30 min in THF at 25°C and 1 atm H_2. The yields decreased only by 2–4% even after the reaction had been continued further for 5 h. The addition of quinoline, which is known to be effective for the selective hydrogenation of alkynes and conjugated dienes,[77] greatly depressed the hydrogenation of 1,5-COD as well as COE, with the results of decreased selectivity.[78] It is noted that the isomerization of 1,5- to 1,4-COD increased to significant extents in the presence of PAA. Since it might be possible that carbon monoxide is formed from PAA on the catalyst surface, Higashijima et al. studied in details the hydrogenation of 1,5-COD with unpoisoned and PAA- and CO-poisoned palladium blacks in THF at 25°C and 1 atm H_2.[75] By applying a computer simulation to the varying composition



Scheme 3.8 Hydrogenation routes of 1,5-cyclooctadiene I.

TABLE 3.3 Rate Constants for the Respective Hydrogenation Route of 1,5-Cyclooctadiene over Pd Catalysts[a,b]

	Rate Constant ($min^{-1}\cdot g\ cat^{-1}$)				
Catalyst	k_1	k_2	k_3	k_4	$k_2/(k_1 + k_4)$
Pd–$CaCO_3$ (Farmakon)[c]	0.30	0.0044	0.08	0.38	0.0065
Pd–$CaCO_3$ (Engelhard)[d]	0.40	0.0044	0.10	0.38	0.0058
Pd–Al_2O_3[e]	0.56	0.0088	0.18	1.5	0.0043

[a]Data of Hanika, J.; Svoboda, I.; Ruzicka, V. *Collect. Czech. Chem. Commun.* **1981**, *46*, 1031. Reprinted with permission from Academy of Sciences of the Czech Republic.
[b]The substrate (1 ml) in 25-ml solution in heptane was hydrogenated at 27°C and 1 atm H_2 using 0.2–1 g of Pd catalyst.
[c]Lindlar catalyst (5% Pd); grain size < 0.05 mm.
[d]Lindlar catalyst; grain size < 0.05 mm.
[e]0.56% Pd on γ-alumina; pellets, 5 mm in diameter, were crushed and screened prior to use (grain size < 0.05 mm).

of reaction mixture versus reaction time with the assumption of a Langmuir–Hinshelwood kinetics (Figs. 3.1*a*–*c*), the kinetic data for the hydrogenation of 1,5-COD and related compounds (Table 3.4) have been determined on the basis of the reaction routes shown in Scheme 3.9. The values of k_4 and k_5 were obtained from the results of the hydrogenation of 1,4-COD in which the rate constant k_4 involved that for the 1,3-COD that would be formed by isomerization of 1,4-COD and hydrogenated to COE apparently without being desorbed.

Over PAA-poisoned palladium k_1 did not decrease but rather increased slightly, compared to that for unpoisoned palladium, while a remarkable decrease in k_1 was observed over CO-poisoned palladium. Both the isomerization of 1,5- to 1,4-COD (k_3) and the isomerization of 1,4- to 1,5-COD (k_5) increased significantly over PAA-poisoned palladium, while both k_3 and k_5 decreased with CO-poisoned palladium. Over both poisoned catalysts, the rate constant for the hydrogenation of COE (k_2) became very small and the hydrogenation to COA was brought to an almost complete halt. The maximum yield of COE was 98.4% over PAA-poisoned palladium and 96.2% over CO-poisoned palladium, compared to 93.5% over unpoisoned palladium. The strength of adsorption of isomeric CODs relative to COE over unpoisoned palladium (shown in parentheses) has been estimated, which was in the order 1,3-COD (33.3) > 1,4-COD (15.7) > 1,5-COD (7.1) > COE (1.0). However, it has been found that, in competitive hydrogenations of 1,5- or 1,4-COD with 1,3-COD over the poisoned catalysts, neither 1,4-COD nor 1,5-COD is hydrogenated at all until 1,3-COD had been completely consumed, in contrast to the hydrogenations over unpoisoned palladium, indicating that the relative reactivity of 1,3-COD to 1,4- or 1,5-COD becomes very large over the poisoned palladium catalysts. These findings were in line with the observation that, during the hydrogenation of 1,4-COD, 1,3-COD was detected in much smaller amounts over PAA-poisoned palladium than over unpoisoned palladium.

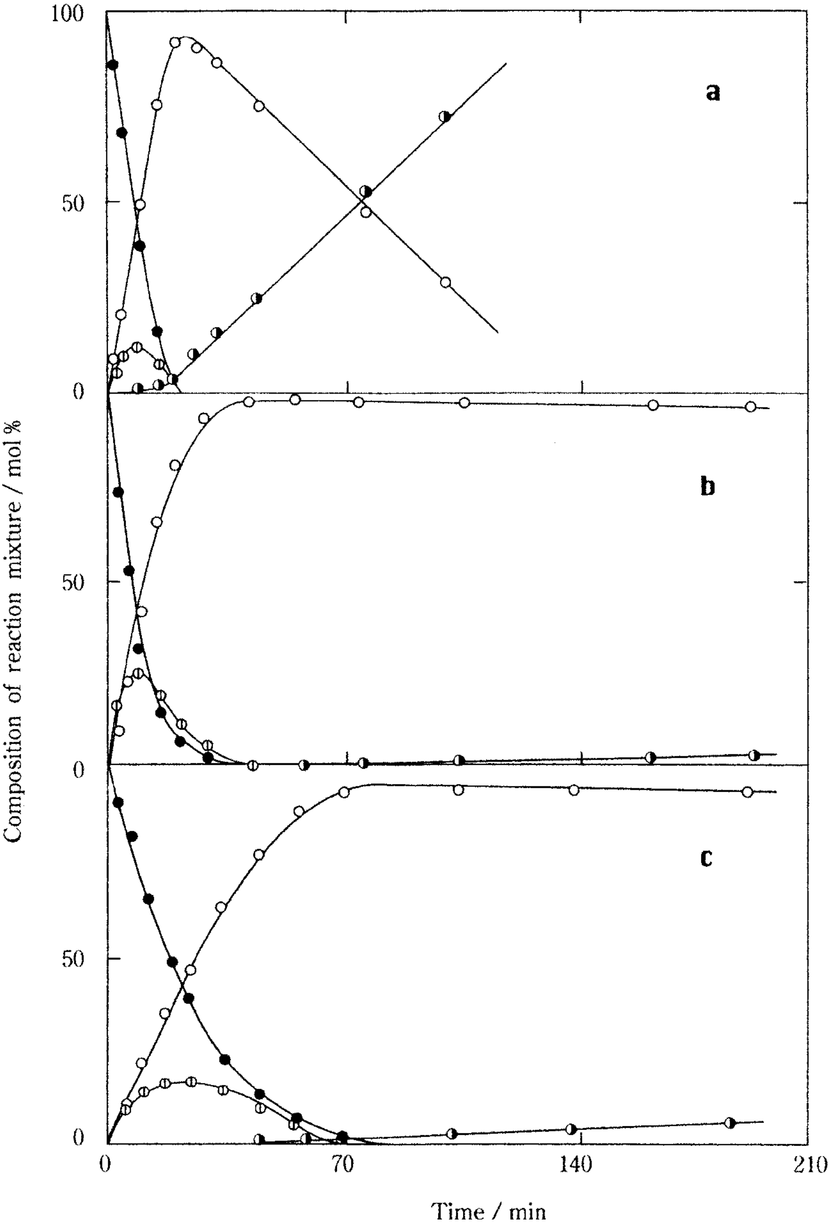


Figure 3.1 The composition of reaction mixture as a function of reaction time in the hydrogenation of 1,5-cyclooctadiene over unpoisoned (a), phenylacetaldehyde-poisoned (b), and carbon monoxide–poisoned (c) palladium catalysts. The points are experimental values, and the curves show the simulations using the values given in Table 3.4. For the reaction conditions, see footnote *b* in Table 3.4. (Key: ● 1,5-COD; ⦶ 1,4-COD; ○ COE; ◑ COA. (For abbreviations, see Scheme 3.9.) (From Higashijima, M.; Hó, S.-M.; Nishimura, S. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 2960. Reproduced with permission of Chemical Society of Japan.)

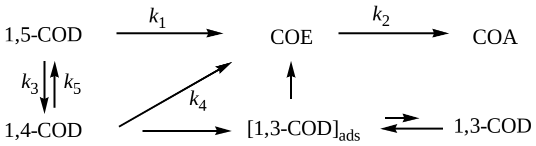
TABLE 3.4 Kinetic Data for the Hydrogenation of 1,5-Cyclooctadiene: Effects of Phenylacetaldehyde and Carbon Monoxide[a,b]

	Rate Constant × 10^3 ($mol \cdot min^{-1} \cdot g\ Pd^{-1}$)					Maximum Concentration (mol %)		Ratio of Adsorption Coefficients	
Catalyst	k_1	k_2	k_3	k_4	k_5	COE	1,4-COD	$b_{1,4}/b_{1,5}$	$b_{COE}/b_{1,5}$
Pd	10.0	1.70	7.0	12.7	0.66	93.5	11.2	2.2	0.14
PAA–Pd[c]	13.6	0.02	30.0	8.3	1.10	98.4	26.1	4.8	0.87
CO–Pd[c]	4.0	0.08	4.4	4.3	0.29	96.2	17.1	2.4	0.35

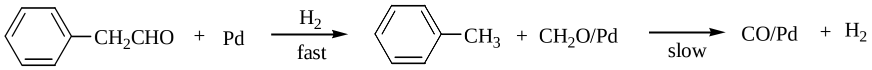
[a]Data of Higashijima, M.; Hó, S.-M.; Nishimura, S. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 2960. Reprinted with permission from Chemical Society of Japan.
[b]1,5-COD (0.4 mmol) was hydrogenated in 6 ml THF over 2 mg of Pd black at 25°C and 1 atm H_2. For the rate constants k_i's, see Scheme 3.9.
[c]After prereduction of the catalyst with H_2 in THF for 20 min, the catalyst was treated with phenylacetaldehyde (196.6 mmol) for 20 min or with CO (3.08 mmol) for 10 min under the atmosphere of hydrogen.

These results suggest that the greater extents of the isomerization of 1,5- to 1,4-COD (and also to 1,3-COD) over PAA-poisoned palladium may have contributed to give the highest maximum yield of COE among the palladium catalysts investigated. Small amounts of toluene, which are formed when the catalyst is pretreated with PAA in the presence of hydrogen prior to hydrogenation, have been found to be associated with the characteristic selectivity of PAA-poisoned palladium. Although the toluene may be formed from PAA together with either formaldehyde or CO (see Scheme 3.10), the different characteristics of PAA- and CO-poisoned catalysts, as described above, favor the view that the PAA-poisoned palladium is actually the catalyst poisoned by the formaldehyde formed on the catalyst surface by hydrogenolysis of PAA. This conclusion has been supported by the observation that an increased isomerization of 1,5- to 1,4-COD and a high selectivity to COE were obtained by the addition of small amounts of a formalin solution to unpoisoned palladium, although the rate of hydrogenation decreased significantly when the formalin solution was added, in contrast to the case with PAA-poisoned catalyst.[79] When PAA-poisoned palladium was used repeatedly, the characteristics of the catalyst in the hydrogenation of 1,5-COD gradually approached the nature of CO-poisoned palladium, suggesting that the formaldehyde formed on palladium was decomposed slowly into CO and hydrogen during the repeated use.

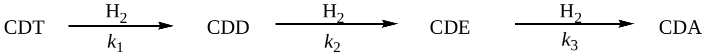
The hydrogenation of 1,5,9-cyclododecatriene (1,5,9-CDT) to cyclododecadienes (CDD) and cyclododecene (CDE) proceeds much less selectively than in the case of 1,5-COD. This may be due to the fact that the three double bonds in 1,5,9-CDT cannot assist each other on adsorption to catalyst, as may be deduced from the inspection of its molecular model. Thus, it is expected that the difference in strength of adsorption or reactivity between 1,5,9-CDT and CDD or CDE would be considerably smaller than that between 1,5-COD and COE. Hanika et al. studied the hydrogenation of 1,5,9-



Scheme 3.9 Hydrogenation routes of 1,5-cyclooctadiene II.



Scheme 3.10 Reactions of phenylacetaldehyde in the presence of Pd catalyst and hydrogen.



Scheme 3.11 Hydrogenation of 1,5,9-cyclododecatriene (CDT) via cyclododecadiene (CDD) and cyclododecene (CDE) as intermediates.

TABLE 3.5 Rate Constants for the Consecutive Hydrogenation of Isomeric 1,5,9-CDT and Maximum Concentrations of CDD and CDE Intermediates[a,b]

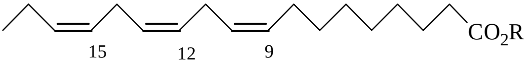
		Rate Constant ($min^{-1} \cdot g\ cat^{-1}$)			Maximum Concentration (wt %)	
CDT	Catalyst	k_1	k_2	k_3	CDD	CDE
Trans, trans, trans	Pd–C[c]	0.06	0.07	0.12	34	18
	Pd–$CaCO_3$[d]	0.025	0.015	0.035	46	17
	Pd–Al_2O_3[e]	0.125	0.08	0.04	45	45
Cis, trans, trans	Pd–C[c]	0.065	0.065	0.25	38	10
	Pd–$CaCO_3$[d]	0.01	0.005	0.003	50	> 46
	Pd–Al_2O_3[e]	0.07	0.029	0.0058	53	65
Cis, cis, trans	Pd–Al_2O_3[e]	0.09	0.045	0.006	50	72

[a]Data of Hanika, J.; Svoboda, I.; Ruzicka, V. *Collect. Czech. Chem. Commun.* **1981**, *46*, 1039. Reprinted with permission from Academy of Sciences of the Czech Republic.
[b]The reaction conditions were the same as those described in Table 3.3, footnote *b*.
[c]3% Pd–C.
[d]Lindlar catalyst (Farmakon, 5% Pd).
[e]0.56% Pd on γ-Al_2O_3.

CDT over 3% Pd–C, 0.56% Pd–γ-Al_2O_3 and Lindlar Pd–$CaCO_3$ (Farmakon, 5% Pd) as catalysts in heptane at 27°C and 1 atm H_2.[80] The kinetic constants for the respective reaction paths described in Scheme 3.11 have been determined, assuming the reactions to be first-order and ignoring the difference in reactivity between the *cis* and *trans* isomers of CDD and CDE intermediates. The results are summarized in Table 3.5. The maximum yields of CDD and CDE, which also depended on the stereoisomeric structure of the CDT hydrogenated, were generally the highest over Pd–Al_2O_3 and the lowest over Pd–C. Over Pd–Al_2O_3, the highest maximum yields of CDE were 72, 65, and 45% with *cis*, *cis*, *trans*-, *cis*, *trans*, *trans*-, and *trans*, *trans*, *trans*-CDT, respectively. In comparison with the hydrogenation of 1,5-COD (Table 3.3), the hydrogenation of 1,5,9-CDT was considerably slower, in particular, with the Lindlar catalyst, and the selectivity with respect to the formation of intermediates was lower, although much higher yields of CDE were reported with palladium or modified palladium catalysts in vapor-phase hydrogenation.[81,82] Very high yields of CDE were also obtained in the hydrogenation with some homogeneous catalysts, where high selectivity appears to result from extensive isomerization prior to hydrogenation of nonconjugated CDT and CDD to conjugated CDT or CDD.[83]

3.5 FATTY ACID ESTERS AND GLYCERIDE OILS

The hydrogenation of fatty oils is one of the most striking industrial applications of catalytic hydrogenation. Normann obtained a patent on liquid-phase hydrogenation for this process in 1903,[84] only 6 years after the discovery by Sabatier and Senderens on the vapor-phase hydrogenation over reduced nickel catalyst.[1] Selective hydrogenation of unsaturated fatty esters such as linolenates (**35**) and linoleates (**36**) is an important reaction which is involved in the industrial process for the hydrogenation of glyceride oils.[2,85,86] Certain aspects of the hydrogenation of vegetable oils and industrial reactors have been reviewed by Allen,[87] Hastert,[88] and Edvardsson and Irandoust.[89] Regio- and stereoselective hydrogenation of **35** to **36** and oleate (**37**) or of **36** to **37**, however, is an extremely difficult transformation, since it is usual that the hydrogenation is accompanied by the formation of positional and geometrical isomers and gives a mixture of isomeric octadecadienoates and octadecenoates. Developments in capillary gas–liquid chromatography (GLC) and $AgNO_3$ thin-layer chromatography (TLC), together with other elaborated instrumental analyses, have made it much easier to separate quantitatively the positional and geometrical isomers of these unsaturated products.[90]



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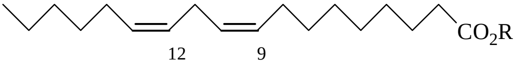

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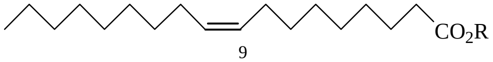

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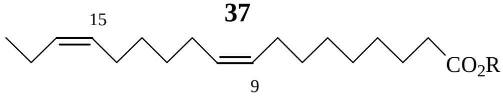

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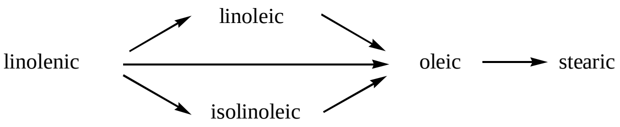
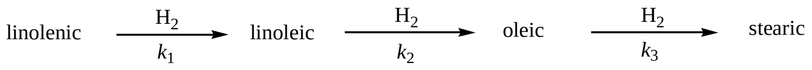
Baily demonstrated that the model shown in Scheme 3.12 could be used to measure the relative rate constants for each hydrogenation step in the batch hydrogenation of linseed, soybean, and cottonseed oil. Isolinoleic represents octadeca-9,15-dienoic species (**38**).[91] Ignoring the apparent simultaneous hydrogenation of two double bonds, Albright calculated the rate constants k_1, k_2, and k_3 for the hydrogenation of linolenic to linoleic, linoleic to oleic, and oleic to stearic acid groups, respectively, on the basis of a model of a simplified set of consecutive reactions (Scheme 3.13) that may represent reasonably well the experimental data of industrial batch hydrogenations of triglycerides containing little or no linolenic acid groups.[92] The varying composition of reaction mixture versus reaction time can be computed from a set of values of k_1, k_2, and k_3. Also, selectivity can be compared quantitatively by the values of k_1/k_2 and k_2/k_3, defined as the selectivity ratios. The selectivity ratio k_1/k_2 may become a criterion for producing an edible oil of improved stability.[93] The values of k_2/k_3 were varied from 2 to 50, the range found for from highly nonselective to highly selective hydrogenations. In a typical example of the hydrogenation of soybean oil over a nickel catalyst at 175°C and 0.11 MPa H_2 where $k_1/k_2 = 2.3$ and $k_2/k_3 = 12.2$, it has been shown that the calculated curves showing the varying composition of the reaction mixture are in excellent accord with the experimental data through a wide range of reaction time (Fig. 3.2).[94] As seen in this example, the rate of hydrogenation of oleic group is usually considerably smaller than those for linolenic and linoleic groups and the hydrogenation proceeds rather selectively.

Figure 3.3 shows the results by Cousins et al. on the distributions of double bonds at different reaction temperatures when methyl linoleate (iodine value = 169.5) was hydrogenated over a nickel catalyst to an iodine value of about 80 where practically all of the linoleate had disappeared.[95] It is seen that in the samples hydrogenated at 170 and 200°C the concentration of the double bonds is greatest at the 10 position and decreases symmetrically as the distance from this position increases, while the greatest concentration of the double bonds was found at the 9 position when the temperature of the hydrogenation was reduced to 140 and 110°C (nonselective conditions). In the run at 110°C, more than 50% of the residual double bonds appeared to be at their original positions. These results as well as those by Allen and Kiess[96] indicate that the dou-



Scheme 3.12 Hydrogenation sequence of linolenate to stearate.



Scheme 3.13 A simplified model for the hydrogenation of linolenate to stearate.

ble bond at the 12 position is hydrogenated somewhat faster than that at the 9 position under nonselective conditions. In general, the operating conditions that tended to increase selectivity and the formation of *trans* isomers (high temperature and low hydrogen pressure or low hydrogen dispersion rate) tended to increase the concentration of double bonds at the 10 position.

Table 3.6 shows the results by Allen and Kiess on the proportion of the *trans* isomers in each positional isomer formed in the hydrogenation of linoleic acid over a nickel catalyst under nonselective and selective conditions.[96] Nonselective conditions result in rather low amounts of *trans* isomers, especially in the 9- and 12-monoenoic acids, while more 9- and 12-*trans* monoenes are formed under selective hydrogena-

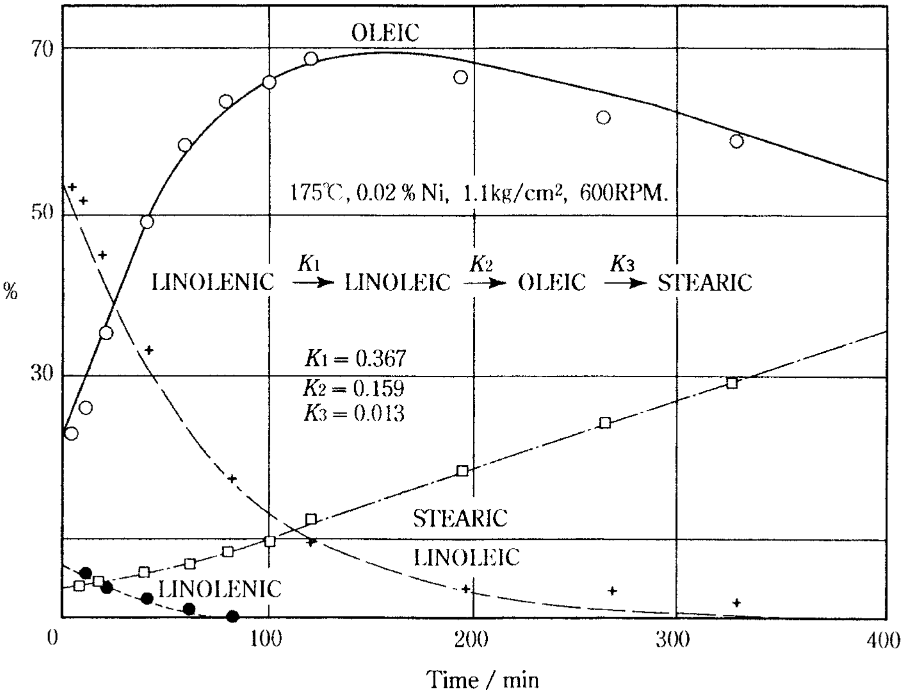


Figure 3.2 The varying composition versus reaction time in the hydrogenation of a soybean oil over nickel catalyst. The points are experimental values and the lines show the curves calculated by using the kinetic constants in the figure. (From Allen, R. R. in *Bailey's Industrial Oil and Fat Products*, 4th ed.; Swern, D., Ed.; Wiley: New York; 1982; Vol. 2, p 12. Reproduced with permission of John Wiley & Sons, Inc.)

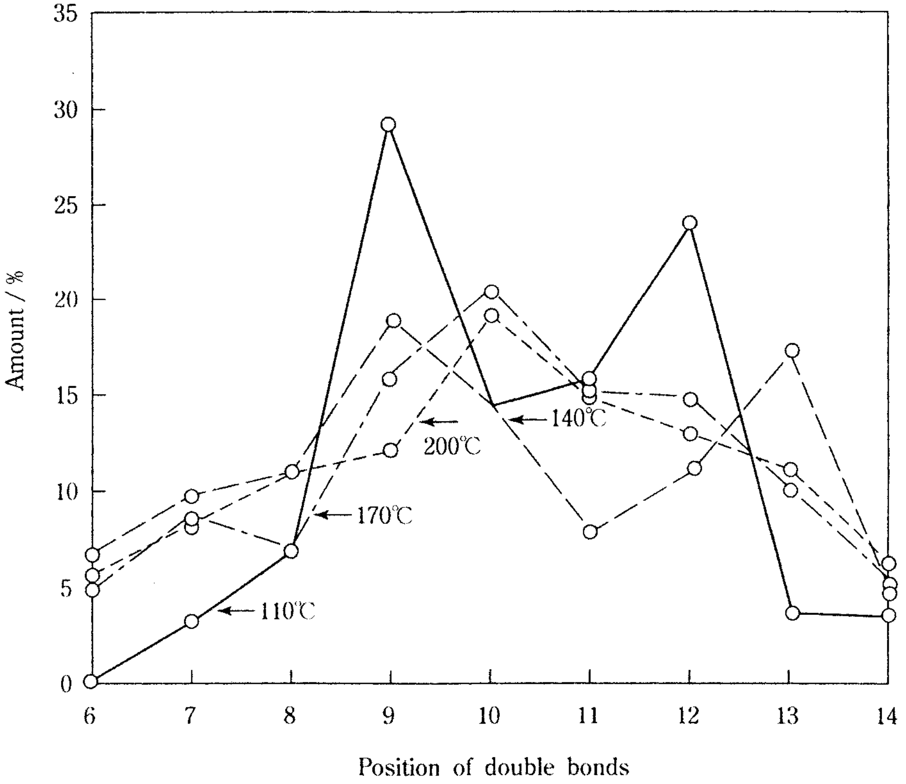


Figure 3.3 Distribution of double bonds at different hydrogenation temperatures. (From Cousins, E. R.; Guice, W. A.; Feuge, R. O. *J. Am. Oil Chem. Soc.* **1959**, *36*, 24. Reproduced with permission of AOCS Press.)

TABLE 3.6 Positional and Geometric Isomers in Monoenoic Acids from Partial Hydrogenation of Linoleic Acid[a]

	Nonselective Hydrogenation[b]		Selective Hydrogenation[c]	
Double-Bond Position	Positional Isomer (%)	Trans Isomer (%)	Positional Isomer (%)	Trans Isomer (%)
12	28.6	25.6	25.1	50.0
11	14.6	57.5	19.8	67.2
10	16.5	65.0	23.1	74.0
9	40.3	17.4	32.0	38.7
Total *trans* (%)		33.5		55.3

[a]Data of Allen, R. R.; Kiess, A. A. *J. Am. Oil Chem. Soc.* **1956**, *33*, 355. Reprinted with permission from AOCS Press.

[b]120°C, 0.13 MPa H_2, 0.5% Ni (from nickel formate).

[c]220°C, 1 atm H_2, 0.5% Ni (from nickel formate).

tion. More *trans* in the 12 isomer than in the 9 isomer may be related to the greater reactivity of the 12 double bond over the 9 double bond as indicated by the greater amounts of the 9-monoene in the monoenoic acids. Under both nonselective and selective conditions, extensive *trans* formation was observed in the 10- and 11-monoenoic acids. It is probable that the isomerization to conjugated dienes, followed by the 1,4 addition, contributed to the formation of the *trans* isomers.[97]

Krishnaiah and Sarkar investigated the effect of chromia on the activity and selectivity of 25% Ni–SiO_2 in the hydrogenation of cottonseed oil (palmtic 22.5, stearic 3.5, oleic 22.5, and linoleic 16.5 mol%) at 120–140°C and 0.5–1 MPa H_2.[98] Chromia was found to suppress the stearate formation completely with its optimum content of 0.17 Cr/Ni atomic ratio. The kinetics of the process was found to be first-order with respect to linoleate and half order with respect to hydrogen.

Kitayama et al. compared the catalytic activity and selectivity of Ni–SiO_2, Ni–Al_2O_3 (5% Ni, prepared by decomposition of nickel formate), Cu–Al_2O_3 (41% Cu), and palladium black in the hydrogenation of linoleic acid at 40°C and 0.039 MPa H_2.[99] The copper catalyst was more selective for monoenoic acid formation than nickel and palladium catalysts; the selectivity for stearic acid formation was only 0.8% at 35.3% conversion, compared with 6.9% on Ni–SiO_2, 8.1% on Ni–Al_2O_3, and 5.2% on palladium at similar conversions. The monoenoic acids in the partial hydrogenation products contained eight positional and geometric isomers. On nickel and palladium catalysts, the yield of *cis*- and *trans*-12-monoenoic acids was larger than that of *cis*- and *trans*-9-monoenoic acids, while the 9-monoenoic acids were found in greater amount than the 12-monoenoic acids on copper. The *trans/cis* ratio of monoenoic acids on the nickel and copper catalysts was 1.1–1.5, while the ratio was much larger (3.7) on palladium.

Alouche et al. studied the selective hydrogenation of rapeseed oil over reduced Ni–Ce oxides and the effects of aluminum incorporation to them. The binary Ce–Ni oxide presented a good selectivity in the partial hydrogenation, as studied in a flow system at temperatures of 190–250°C, but with a large *Z/E* isomerization. On the other hand, use of ternary Ce–Ni–Al oxides [e.g., Ce/Al = 1, Ni/(Ce + Al) = 5], prepared from the nitrates of cerium, nickel, and aluminum by coprecipitation using potassium hydroxide, allowed a decrease in the extent of the *Z/E* isomerization.[100]

Copper catalysts have been found to be more selective than nickel, platinum, or palladium for the hydrogenation of linolenate in soybean oil.[101] Koritala et al. studied the hydrogenation of methyl linolenate over copper–chromium oxide at 150°C and atmospheric pressure and found that the dienes formed from linolenate consisted mostly of conjugated dienes, compared to only traces of conjugated diene formed with nickel catalyst. About 16% of the unreduced trienes had also diene conjugation. The high selectivity of the copper catalyst has been explained by first isomerization of linolenate to form conjugated double bonds that are hydrogenated to form conjugated and nonconjugated dienes.[101] Kirschner and Lowrey compared the hydrogenation of trilinolein over a copper–chromium oxide promoted with manganese and a nickel catalyst promoted with zirconium at 171–200°C and 0.28–0.69 MPa H_2. The copper catalyst produced essentially no

saturates and gave fewer diene and more monoene isomers, particularly *trans* monoenes, than did the nickel catalyst.[102] Koritala[103,104] and Johansson[105] studied the hydrogenation of soybean and rapeseed oils using Cu–SiO_2 catalysts prepared by adding ammonium hydroxide in excess to an aqueous copper(II) nitrate trihydrate to dissolve the copper hydroxide precipitate formed, followed by the addition of silica gel. The copper catalysts thus prepared were more resistant to reduction to the metal than copper–chromium oxide, and found to be superior to copper–chromium oxide in rapeseed oil hydrogenation. In soybean oil, however, the two types of catalyst showed similar activities.

Bautista et al. studied the effects of various supports and solvents on the selective hydrogenation of ethyl linoleate to ethyl oleate over nickel and nickel–copper catalysts.[106] Most hydrogenations were carried out at 50°C and 0.41 MPa H_2 in methanol in which the best results were obtained with respect to catalytic activity and selectivity. The supports compared included sepiolite, a hydrous magnesium silicate (a clay mineral), SiO_2, Al_2O_3, active carbon, and three different $AlPO_4$, and three commercial nickel catalysts were used as a reference. The influence of copper as a second metal in improving the selectivity has been found to be closely related to its influence in the relative adsorption coefficients of linoleate to oleate. The best selectivity was obtained $AlPO_4$-supported nickel–copper (20/0.3 proportion) as catalyst.

Studies on the hydrogenation of fatty acids and oils over platinum group metals have been reviewed by Rylander.[107] Zajcew studied the hydrogenation of tall oil fatty acids over carbon-supported platinum metals in methanol at 28°C and atmospheric hydrogen pressure.[108] The activity increased in the order Ru < Ir < Pt < Rh < Pd. The tendency to form *trans* isomers increased in the order Pt < Ir < Ru < Rh < Pd, which is the same with the generally recognized order of platinum metals toward double-bond migration.[30,31] The selectivity increased in the order Ir < Ru < Pt < Rh < Pd, which was also the same with the order in the *trans* formation except for platinum. Palladium more highly dispersed on carbon was found more active and more selective. Thus, 1% Pd–C was more active and more selective than 5% Pd–C. The effect of catalyst concentration on the rate of hydrogenation of 70% soybean–30% cottonseed oil was studied with 0.5% Pd–C as catalyst at 185°C and atmospheric pressure. The results shown in Table 3.7 indicate that over the highly active palladium catalyst the rate was controlled by diffusion process, especially in the region of high catalyst concentrations. The effectiveness of Pd–C catalyst has been demonstrated in pilot-plant hydrogenations of soybean oil to shortening stocks (corresponding to the decrease in iodine number from 127 to ~80) at 80–121°C and around 0.3 MPa H_2.[109] In three combined experiments with repeated reuse, 1g of 5% Pd–C could hydrogenate about 18 kg of oil to a satisfactory product; and 1 g of 2% Pd–C, about 11 kg of oil.

Riesz and Weber compared the selectivities of commercial platinum, palladium, rhodium, and nickel catalysts for hydrogenation of linolenic components in soybean oil.[110] Representative results are summarized in Table 3.8. Certain platinum metal catalysts showed higher selectivities than nickel catalysts, as indicated by the values of S_L (k_1/k_2 in Scheme 3.13) = 2.4–2.7. Generally, nickel catalysts showed selectivities

TABLE 3.7 Effect of Catalyst Concentration on Rate in the Hydrogenation of a Glyceride Oil over Pd–C[a,b]

% Pd in Oil	Catalyst Functioning Rate[c]
0.1	18
0.02	40
0.005	72
0.0025	130
0.00125	215
0.0005	354

[a]Data of Zajcew, M. *J. Am. Oil Chem. Soc.* **1960**, *37*, 11. Reprinted with permission from AOCS Press.
[b]Catalyst, 0.5% Pd–C; temperature, 185°C; pressure, atmospheric; agitation, 620 rpm; 70% soybean–30% cottonseed oil.
[c]Iodine units reduction per min per 1% of catalytic metal.

below $S_L = 2.0$, although Raney Ni afforded higher values. The selectivity of platinum catalysts decreases markedly at low temperatures.[111] At elevated temperatures, however, platinum becomes as selective as palladium catalysts. The highest activity and S_L selectivity were obtained with 0.2% Pd–C at 150°C. With nickel catalysts, there was an optimum temperature for selectivity that occurred at 100°C for 63.5% Ni–kieselguhr. *Trans* isomers were in the range of 7.8–15.4% for the platinum metal catalysts, while nickel catalysts provided a lesser degree of isomerization, 5.2–7.4% *trans* for the most selective catalysts. Hsu et al. compared the activity and selectivity of three palladium catalysts supported on carbon, alumina, and barium sulfate in the hydrogenation of soybean and canola oil. The effect of temperature (50–110°C), hydrogen pressure (0.4–5.2 MPa), catalyst concentration (95–100 ppm), and starting oil on the reaction rate, *trans*–isomer formation, and selectivity has been studied;[112] 5% Pd–Al_2O_3 showed higher activity and lower *trans* isomerization (see the results in Table 3.8 on palladium catalysts). At 70°C, 5.2 MPa H_2 and 50 ppm Pd, only 9.4% *trans* were formed when canola oil was hydrogenated to an iodine value of 7.4. In general, high pressure and low temperature favored low *trans* formation with no appreciable decrease in catalytic activity.

Nishimura et al. noticed during a study on the hydrogenation of methyl linolenate that unpurified methyl linolenate was selectively hydrogenated to methyl octadecenoates over palladium catalysts, with practically no further hydrogenation to methyl stearate. Although the effective principle in the unpurified linolenate could not be identified, it has been found that, among various aldehydic compounds studied, the addition of a small amount of phenylacetaldehyde depressed the hydrogenation of methyl linoleate to methyl stearate almost completely, similarly as in the hydrogenation of 1,5-cyclooctadiene, where the hydrogenation of cyclooctene to cyclooctane was almost completely inhibited with phenylacetaldehyde (see Fig 3.1*b*).[76] The effects of addition of various aldehydes and quinoline are shown in Table 3.9.

TABLE 3.8 Selective Hydrogenation of Soybean Oil with Platinum Metals and Nickel Catalysts[a,b]

Catalyst[c]	Temperature (°C)	Rate (mmol/min)	Selectivity Index[d] S_O	S_L	*Linolenic Removed* (%)	Trans Isomers (%)
5% Pt–C (A)	35	0.28	0.1	0.1	6	0.7
	100	0.51	4.6	1.3	30	8.0
	150	0.70	25.6	1.4	48	13.2
5% Pt–C (B)	150	0.58	large	2.7	52	12.8
1% Pt–SiO_2	150	0.62	6.0	2.6	46	7.8
0.5% Pt–Al_2O_3	100	0.74	10.5	2.3	46	4.5
5% Pd–C	35	0.36	4.6	1.1	24	5.7
	100	0.97	40.5	2.5	52	13.8
5% Pd–$BaSO_4$	100	1.46	19.5	1.7	42	6.2
1% Pd–SiO_2	100	0.55	6.0	2.6	46	7.8
0.5% Pd–Al_2O_3	100	1.20	108.0	2.3	52	11.4
0.2% Pd–C	150	1.54	83.2	2.9	62	15.4
5% Rh–C	100	0.57	23.8	2.7	50	15.4
0.5% Rh–Al_2O_3	100	0.86	330.0	2.6	54	13.8
65% Ni–kieselguhr	100	1.06	19.7	2.0	42	5.6
	150	2.33	4.3	0.8	30	8.6
27% Ni–flakes	150	0.53	15.6	1.6	40	6.2
Raney Ni	50	0.29	14.2	2.5	48	6.5
	150	1.34	18.5	2.1	50	5.7

[a]Data of Riesz, C. H.; Weber, H. S. *J. Am. Oil Chem. Soc.* **1964**, *41*, 400. Reprinted with permission from AOCS Press.
[b]The composition of soybean hydrogenated was 10.0% palmitic, 3.0% stearic, 27.1% oleic, 54.9% linoleic, and 5.0% linolenic.
[c]The metal concentration was 0.025 wt% for the noble metal catalyst and 1.3 wt% for the nickel catalysts, based on the oil.
[d]S_O and S_L: the relative rates of linolenic to oleic and linolenic to linoleic components, respectively.

It is seen that the selectivity, as estimated in terms of the ratio of the rate of disappearance of linoleate (V_D) to the rate of disappearance of octadecenoates (V_M), becomes very large with addition of phenylacetaldehyde. In the presence of phenylacetaldehyde methyl octadecenoates were obtained in maximum yields of 99.1% over Pd–$CaCO_3$ and 98.8% over palladium black in hydrogenation in THF at 25°C and atmospheric hydrogen pressure. The formation of stearate was still of very low level even after 5 h of reaction, as indicated by 92.4 and 90.7%, respectively, of octadecenoates remaining in the reaction mixture. The high selectivity was also obtained in the hydrogenation in cyclohexane, but use of *t*-butyl alcohol as solvent lowered the effect of phenylacetaldehyde markedly. Quinoline, the addition of which is known to be effective for selective hydrogenation of alkynes and conjugated dienes,[113] greatly depressed the hydrogenation of both linoleate and octadecenoates, resulting in a very low value of V_D/V_M and only an 84.6% maximum yield of octadecenoates.

TABLE 3.9 Effects of Additives on the Hydrogenation of Methyl Linoleate over Palladium Catalysts[a,b]

Catalyst	Solvent	Additive[c]	V_D/V_M^d	Octadecenoate Concentration (%)[e] At Maximum	After 5 h
5% Pd–$CaCO_3$	THF	—	25	95.4	0.0
5% Pd–$CaCO_3$	THF	Benzene	59	97.5	18.9
5% Pd–$CaCO_3$	THF	PhCHO	45	97.7	63.8
5% Pd–$CaCO_3$	THF	$PhCH_2CHO$	520	99.1	92.4
5% Pd–$CaCO_3$	THF	$Ph(CH_2)_2CHO$	56	97.9	29.8
5% Pd–$CaCO_3$	THF	$Ph(CH_2)_3CHO$	43	98.0	45.3
5% Pd–$CaCO_3$	THF	$CH_3(CH_2)_2CHO$	24	96.0	0.0
5% Pd–$CaCO_3$	Cyclohexane	$PhCH_2CHO$	Very large	98.6	98.6
5% Pd–$CaCO_3$	*t*-BuOH	$PhCH_2CHO$	58	97.3	59.4
5% Pd–$CaCO_3$	THF	Quinoline	3	84.6	64.6
Pd black	THF	—	3	93.2	0.0
Pd black	THF	$PhCH_2CHO$	230	98.8	90.7

[a]Data of Nishimura, S.; Ishibashi, M.; Takamiya, H.; Koike, N. *Chem. Lett.* **1987**, 167. Reprinted with permission from Chemical Society of Japan.
[b]Methyl linoleate (0.3 mmol) was hydrogenated with 6 mg of 5% Pd–$CaCO_3$ or 3 mg of Pd black in 1.6 ml of solvent at 25°C and atmospheric hydrogen pressure.
[c]The additive (0.2 mmol; 0.02 mmol for quinoline) was added to prereduced catalyst before the addition of substrate.
[d]V_D: the rate of disappearance of methyl linoleate; V_M: the rate of disappearance of methyl octadecenoates.
[e]GC analysis.

3.6 CONJUGATED DOUBLE BONDS

3.6.1 Aryl-Substituted Ethylenes

Zartman and Adkins hydrogenated various phenyl-substituted ethylenes with Ni–kieselguhr and copper–chromium oxide as catalysts.[114] The pressure of hydrogen as well as the temperature had a marked effect on the rate of hydrogenation, which depended on the structure of ethylenic linkages. Phenylethylene (styrene) was readily hydrogenated over the nickel catalyst at 20°C and a low pressure of 0.25 MPa H_2 (eq. 3.14). Hydrogenation of 1,2-diphenylethylene (stilbene) (18 g, 0.10 mol) over 2 g Ni–kieselguhr at 20°C required 15 min at 9.3 MPa H_2, 30 min at 3 MPa H_2, and 80 min at 0.27 MPa H_2, while hydrogenation of 1,1,2-triphenylethylene at 20°C required 150 min at 9.5 MPa H_2 and hydrogenation of tetraphenylethylene required over 2 h even at 100°C and 12.5 MPa H_2 (eq. 3.15). In hydrogenations at 125–170°C, these phenylethylenes may give the corresponding cyclohexylethanes. Over copper–chromium oxide these phenyl-substituted ethylenes are hydrogenated rapidly at 125–150°C and 12.5–13.5 MPa H_2 without affecting the phenyl groups. An example is shown in eq. 3.16.

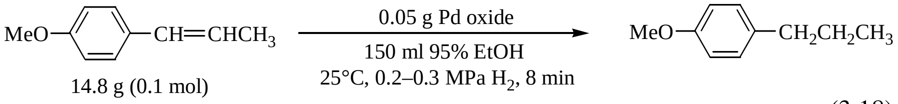
$$\underset{21\text{ g }(0.20\text{ mol})}{PhCH{=}CH_2} \xrightarrow[20°C,\ 0.25\text{ MPa }H_2,\ 75\text{ min}]{2\text{ g Ni–kieselguhr}} \underset{\text{quantitative}}{PhCH_2CH_3} \quad (3.14)$$

$$\underset{12\text{ g }(0.036\text{ mol})}{Ph_2C{=}CPh_2} \xrightarrow[75\text{ ml }C_7H_{14};\ 100°C,\ 12.5\text{ MPa }H_2,\ 2.2\text{ h}]{2\text{ g Ni–kieselguhr}} \underset{\text{quantitative}}{Ph_2CHCHPh_2} \quad (3.15)$$

$$\underset{12\text{ g }(0.036\text{ mol})}{Ph_2C{=}CPh_2} \xrightarrow[75\text{ ml }C_7H_{14};\ 150°C,\ 13.3\text{ MPa }H_2,\ 15\text{ min}]{1\text{ g Cu–Cr oxide}} \underset{\text{quantitative}}{Ph_2CHCHPh_2} \quad (3.16)$$

Over palladium catalysts, phenyl-substituted ethylenes are hydrogenated more readily than the corresponding alkyl-substituted ethylenes, as noted previously. Poor activity of palladium toward the hydrogenation of the aromatic ring at low temperature allows the olefinic bonds to be hydrogenated selectively. Stilbene is hydrogenated smoothly to 1,2-diphenylethane over palladium oxide in ethanol at 25°C and 0.2–0.3 MPa H_2 (eq. 3.17).[5] Anethole (*p*-1-propenylanisole) was hydrogenated faster over palladium oxide (8 min) (eq. 3.18) than over platinum oxide (14 min).[5] Raney Ni behaves similarly to palladium for aryl-substitutions, although to a lesser extent than in the case of palladium.[9,10]

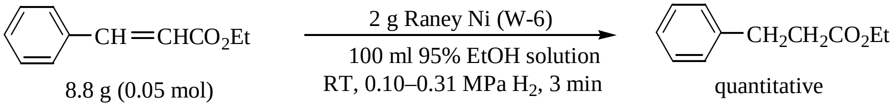
$$\underset{18\text{ g }(0.1\text{ mol})}{PhCH{=}CHPh} \xrightarrow[150\text{ ml }95\%\text{ EtOH};\ 25°C,\ 0.2\text{–}0.3\text{ MPa }H_2,\ 1.2\text{ h}]{0.10\text{ g Pd oxide}} PhCH_2CH_2Ph \quad (3.17)$$



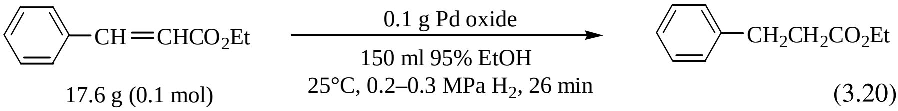
(3.18)

3.6.2 α,β-Unsaturated Acids and Esters

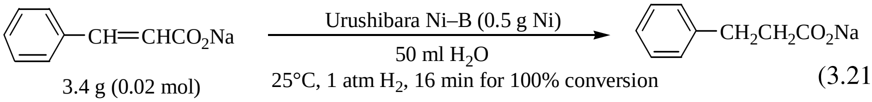
The C–C double bonds conjugated with carboxyl functions are usually much more readily hydrogenated than usual olefinic bonds, especially with nickel and palladium catalysts. Ethyl cinnamate is rapidly hydrogenated over Raney Ni under mild conditions (eq. 3.19).[115] It is also hydrogenated over palladium oxide much faster (eq. 3.20) than over platinum oxide with which 2.9 h were required under the same conditions.[5] Cinnamic acid was hydrogenated smoothly to dihydocinnamic acid as the sodium salt over Urushibara Ni in water under ordinary conditions (eq. 3.21).[116]



(3.19)



(3.20)

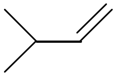
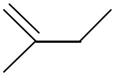
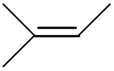
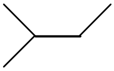
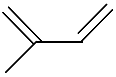


(3.21)

3.6.3 Conjugated Dienes

Conjugated dienes are usually more reactive than simple olefins. However, selectivity in the formation of monoenes depends greatly on the catalyst employed. Kazanskii et al. studied the selectivity in the hydrogenation of isoprene over platinum black, palladium black, and Raney Ni in ethanol at room temperature and atmospheric pressure (Table 3.10).[117] Selectivity for monoenes was much higher over palladium and Raney Ni than over platinum. The monoenes were a mixture of three isomeric methybutenes formed by apparent 1,2, 3,4, and 1,4 additions of hydrogen to isoprene over all the catalysts. The high selectivity for the monoene formation of palladium and Raney Ni was also demonstrated in the hydrogenation of 2,5-dimethyl-2,4-hexadiene in ethanol

TABLE 3.10 The Products (%) in Half-Hydrogenation of Isoprene over Platinum, Palladium, and Raney Ni[a]

Product	Pt	Pd	Raney Ni
	7	25	16
	26	30	40
	15	41	40
	26	2	2
	26	2	2
Selectivity for monoenes (%)	65	98	98

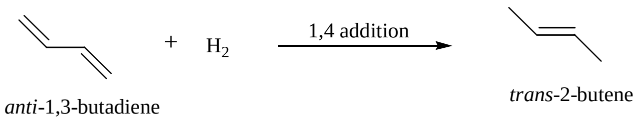
[a]Kazanskii, B. A.; Gostunskaya, I. V.; Granat, A. M. *Izv. Akad. Nauk SSSR, Otdel. Khim. Nauk* **1953**, 670 (*CA* **1954**, *48*, 12664a).

at room temperature and atmospheric pressure.[118] Addition of one molar equivalent (1 equiv) of hydrogen to the diene gave the monoenes in 92 and 99% yields with palladium and Raney Ni, respectively, compared to 75% yield over platinum. However, in contrast to the results with isoprene, the greater part of the monoenes was 2,5-dimethyl-2-hexene, the product resulting from 1,2-addition of hydrogen, which amounted to 86% over palladium and 90% over Raney Ni.

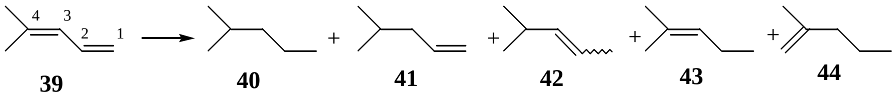
Bond and Wells studied the selectivities of supported group VIII (groups 8–10) metals in the vapor-phase hydrogenation of 1,3-butadiene.[29,30] Palladium, iron, cobalt, and nickel were all perfectly selective for butene formation, and the selectivity decreased in the order: Pd >> Ru > Rh ≥ Pt > Ir. The *trans*/*cis* ratios of the 2-butene formed from 1,3-butadiene over cobalt and palladium were much greater (>10) than those of the 2-butene obtained in 1-butene hydroisomerization. The results sharply contrasted to those obtained over the other metals where almost the same *trans*/*cis* ratios of much smaller values (nearly between 1 and 2) were obtained from both 1,3-butadiene and 1-butene. Formation of the high *trans*/*cis* ratios of 2-butene over cobalt and palladium was explained by 1,4 addition of hydrogen to the 1,3-butadiene adsorbed in *s*-*trans* conformation as shown in Scheme 3.14.

Later studies by Wells and co-workers, however, showed that the *trans*/*cis* ratios of the 2-butene formed from hydrogenation of 1,3-butadiene over nickel and cobalt catalysts depended on the reduction temperature employed for catalyst activation. High *trans*/*cis* ratios of 3.5–8 were obtained over the catalyst reduced at 400°C, while the ratios decreased to ~2 with the catalysts activated below 350°C.[119,120] The characteristic properties of the nickel and cobalt catalysts activated at 400°C were attributed to a modification of the catalysts caused by the sulfur compounds contained in the support that occurred at such a high reduction temperature as 400°C.[121]

Imaizumi et al. studied the hydrogenation of 1,4-dialkyl-1,3-cyclohexadienes over the nine group VIII (groups 8–10) metals and copper in ethanol at room temperature and atmospheric pressure.[122] The selectivity for monoenes formation at 50% conversion increased in the order: Os–C, Ir–C < Ru–C, Rh–C, Pt < Pd–C, Raney Fe, Raney Co, Raney Ni, Raney Cu (= 100%). The selectivity for 1,4-addition product increased in the order Os–C, Ir–C < Ru–C, Rh–C, Raney Cu, Raney Fe, Raney Ni < Raney Co, Pd–C, Pt. Extensive formation of 1,4-dialkylbenzenes (more than 50% with the 1,3-dimethyl derivative) was observed over Raney Ni and Pd–C, while they were not formed over Raney Cu, Os–C, and Ir–C. In the hydrogenation of 4-methyl-1,3-pentadiene (**39**) (Scheme 3.15) over group VIII metals in cyclohexane at room temperature and atmospheric pressure, high selectivity to monoenes was obtained with iron, nickel, cobalt, and palladium catalysts where the amounts of the saturate 2-methylpen-



Scheme 3.14 Formation of *trans*-2-butene via 1,4 addition of hydrogen to adsorbed *s*-*trans*-1,3-butadiene.



Scheme 3.15 Products in partial hydrogenation of 4-methyl-1,3-pentadiene.

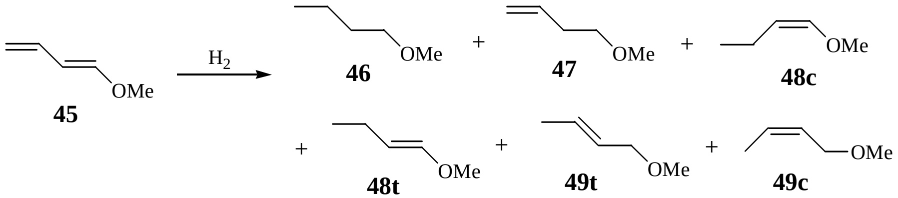
tane (**40**) in the product at 50% conversion was less than 4%, while over the platinum metals other than palladium **40** was formed in as much amounts as 18–46% (Table 3.11).[123] Among the monoenes **41**–**44** formed, the 3,4-addition product **41** increased in the order Os, Ir < Ru, Rh, Pt < Pd, Fe, Ni < Co. The results on cobalt catalysts that the monoene **41** was formed in more than 80% selectivity appear rather unusual, since it indicates that the more hindered double bond in **39** was hydrogenated predominantly. On the other hand, over osmium the 1,2 addition to give **43** took place in 82% selectivity, compared to only a few percents over cobalt catalysts.

Bell et al. studied the hydrogenation of *trans*-1-methoxy-1,3-butadiene (**45**) over Adams platinum, Lindlar palladium, Raney Ni (W-6), and nickel boride (P-2) as catalysts (Scheme 3.16).[124] Table 3.12 compares the products at the hydrogen uptake of approximately one molar equivalent of hydrogen in the hydrogenation of **45** at 30°C and initial hydrogen pressure of 0.36 MPa. Over Adams platinum formation of 1-methoxybutane was significant from the beginning of hydrogenation, while Raney Ni and Lindlar catalyst gave only small amounts of the saturated ether and no hydro-

TABLE 3.11 Selectivity of Group VIII Metals in the Hydrogenation of 4-Methyl-1,3-pentadiene[a,b]

		Product (%)[c]				
Catalyst	Amount (mg)[d]	**40**	**41**	**42**	**43**	**44**
Raney Ni	50	1	50	26	18	5
Ni[e]	100	4	40	28	28	t
Raney Co	500	2	91	6	1	0
Co[e]	1000	3	82	9	6	t
Raney Fe	500	2	47	22	25	4
Pd	5	2	49	20	23	6
Rh	5	44	8	11	34	3
Ru	5	42	4	8	44	2
Pt	5	45	22	14	19	0
Ir	5	46	2	2	50	0
Os	5	18	0	0	82	0

[a]Data of Imaizumi, S.; Muramatsu, I. *Shokubai* **1981**, *23*, 132. Reprinted with permission from Catalysis Society of Japan.
[b]4-Methyl-1,3-pentadiene (0.5 mmol) was hydrogenated in 3 ml of cyclohexane at room temperature and atmospheric pressure.
[c]The product was analyzed at 50% conversion. For the compound numbers, see Scheme 3.15.
[d]Weighed wet for the Raney catalysts and as oxides for reduced nickel and cobalt catalysts.
[e]Prepared by hydrogen reduction of metal oxides.



Scheme 3.16 Products of the hydrogenation of *trans*-1-methoxy-1,3-butadiene.

genolysis products. The predominant product over Adams platinum and Lindlar catalyst was **48t**, the 3,4-addition product, which amounted to 71% with Lindlar catalyst. Raney Ni gave nearly equal amounts of 1,2-, 3,4-, and 1,4-addition products, **47**, **48**, and **49**, respectively. Nickel boride catalyst gave the results similar to those over Adams platinum except that no *cis*-1-methoxy-1-butene (**48c**) was formed over this nickel, indicating no isomerization of **48t** taking place during hydrogenation.

The selective hydrogenation of cyclopentadiene to cyclopentene has been studied not only from an academic interest but also from an industrial viewpoint for the utilization of the C_5 fraction of naphtha cracking products.[125] Cyclopentadiene is hydrogenated readily to cyclopentane over Raney Ni in alcoholic solvents at 25°C and atmospheric pressure. The hydrogenation, however, slows down after uptake of 1 equiv of hydrogen in hydrocarbon solutions.[126] In methanol or ethanol the addition of amines is effective to depress the hydrogen uptake of the second stage.[127,128] Addition of methylamine practically stopped the hydrogenation of cyclopentadiene after absorption of 49% of the theoretical amount of hydrogen, although on repeated hydro-

TABLE 3.12 Products of Partial Hydrogenation of *trans*-1-Methoxy-1,3-Butadiene[a,b]

Catalyst	% Reaction[d]	Composition of Reaction Mixture (%)c						
		46	**47**	**48c**	**48t**	**49t**	**49c**	**45**
Adams Pt	49.8	27.2	6.6	9.8	30.0	9.2	4.4	12.7
Pd–$CaCO_3$ (Lindlar)	50[e]	5.3	2.0	8.8	71.1	11.8	1.0	0.0
Raney Ni (W-6)	45	3.8	32.2	2.3	27.5	21.2	6.8	6.1
Ni boride (P-2)	57	16.4	4.5	0.0	50.5	20.4	8.2	0.0

[a]Data of Bell, J. M.; Garrett, R.; Jones, V. A.; Kubler, D. G. *J. Org. Chem.* **1967**, *32*, 1307. Reprinted with permission from American Chemical Society.
[b]*trans*-1-Methoxy-1,3-butadiene (10 g) was hydrogenated at 30°C and the initial hydrogen pressure of 0.36 MPa over 0.04 g Adams Pt or 0.06 g Lindlar catalyst (with 0.06 g of quinoline). The Raney Ni (W-6) was transferred to the reaction mixture by several portions of methanol, which totaled 20 ml. The Ni boride suspension, prepared from 1.244 g $Ni(OAc)_2{\cdot}4H_2O$ in 40 ml 95% EtOH and 0.38 g $NaBH_4$ in 10 ml 95% EtOH, was transferred to the hydrogenation flask along with 10.38 g of methoxybutadiene.
[c]For the compound numbers, see Scheme 3.16. No butane and butenes were observed for the hydrogenations over the catalysts other than Adams platinum.
[d]The percent reaction is based on the calculated pressure drop for 2 mol of hydrogen per mole of diene.
[e]The hydrogen uptake nearly ceased after 50% reaction.

genation cyclopentadiene was hydrogenated to cyclopentane. With addition of dimethylamine cyclopentene was fully hydrogenated. Ethylenediamine stopped the hydrogenation after absorption of 49–51% of the theoretical amount of hydrogen and the selectivity was retained on repeated hydrogenation. Hexamethylenediamine, piperidine, 4-ethylpyridine, and α-picoline behaved as ethylenediamine, while with 2-ethylpyridine the hydrogenation went to cyclopentane.[128]

Kripylo et al. studied the hydrogenation of cyclopentadiene in vapor phase over group VIII transition metals supported on 25% CaO–γ-Al_2O_3. Palladium and cobalt catalysts showed good selectivity with selectivity ratios (the relative reactivity of cyclopentene to cyclopentadiene) of 0.13 at 80°C to 0.26 at 140°C for palladium and 0.14 at 100°C to 0.37 at 160°C for cobalt, while supported platinum, rhodium, iridium, and nickel catalysts were less selective with selectivity ratios of mostly 1–2.5 for rhodium, iridium and nickel and 5–9 for platinum.[129] In a patent the selectivity of Pd–$CaCO_3$ was improved by treating with a solution containing a heavy-metal ion such as zinc acetate solution.[130] Hirai et al. obtained high yields (98.5–98.7%) of cyclopentene at 100% conversion of cyclopentadiene, using a colloidal palladium prepared by refluxing Pd(II) chloride and poly(*N*-vinyl-2-pyrrolidone) in methanol (Pd–PVP–MeOH/NaOH) in the presence of sodium hydroxide[131] or over colloidal palladium protected with sodium salt of polyacrylic acid and then modified with polyethylenimine, in methanol at 30°C and atmospheric hydrogen pressure.[132] Similar high selectivity to cyclopentene was also obtained, using colloidal palladium supported on a chelate resin with iminodiacetic acid moieties attached to a styrene–divinylbenzene copolymer matrix.[133] The high maximum yields were shown to result from a large difference in strength of adsorption between cyclopentadiene and cyclopentene over these colloidal catalysts. It is noted that the cyclopentene formed is further hydrogenated, although slowly, after cyclopentadiene has been consumed almost completely.

Compared to cyclopentadiene, 1,3-cyclooctadiene appears to be more selectively hydrogenated to cyclooctene, since hydrogenation of the cyclooctene produced may be depressed almost completely over selective palladium catalysts such as Pd–PVP–MeOH/NaOH[74] and PAA- or CO-poisoned palladium.[75] The maximum yields of cycloalkene obtained were higher with 1,3-cyclooctadiene than with cyclopentadiene or with 1,4- and 1,5-cyclooctadiene, as seen from the results in Table 3.13. The yields of cyclooctene were lower with a commercial 5% Pd–C or unpoisoned palladium. Over these unpoisoned catalysts the cyclooctene formed was further hydrogenated to cyclooctane, although in slower rates than the cyclooctadiene.

Selective hydrogenation of $\Delta^{5,7}$-steroids to 5α-Δ^7-steroids is best achieved by hydrogenation with Raney Ni, since the isomerization of Δ^7 to $\Delta^{8(14)}$ in 5α-steroids, which tends to occur over platinum and palladium catalysts (see Scheme 3.6), can be avoided over Raney Ni.[134,135] Thus, Ruyle et al. hydrogenated a number of $\Delta^{5,7}$-steroids with Raney Ni at room temperature and 0.1–0.3 MPa H_2 and obtained pure Δ^7 derivatives in 80–90% yields. Ergosterol acetate was smoothly hydrogenated in benzene to give 3β-acetoxyergosta-7,22-diene in 90% yield (eq. 3.22).[135] Similarly, the Δ^5 double bond of 3β-acetoxypregna-5,7-dien-20-one, methyl 3β-acetoxybisnorchola-5,7-dienate, and 3β-acetoxyisospirosta-5,7-diene (7-dehydrodiosgenin acetate)

TABLE 3.13 Yields of Cyclooctene (%) from Hydrogenation of Isomeric Cyclooctadienes over Palladium Catalysts[a,b]

	Catalyst			
Cyclooctadiene	Pd–PVP–MeOH/NaOH[a,c]	PAA-Poisoned Pd[b,d]	CO-Poisoned Pd[b,d]	Pd[b,d]
1,3-	99.9	99.4	99.7	98.8
1,4-	94.0	98.3	98.0	95.2
1,5-	97.8	98.4	96.2	93.5[e]

[a]Data of Hirai, H.; Chawanya, H.; Toshima, N. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 682. Reprinted with permission from Chemical Society of Japan.

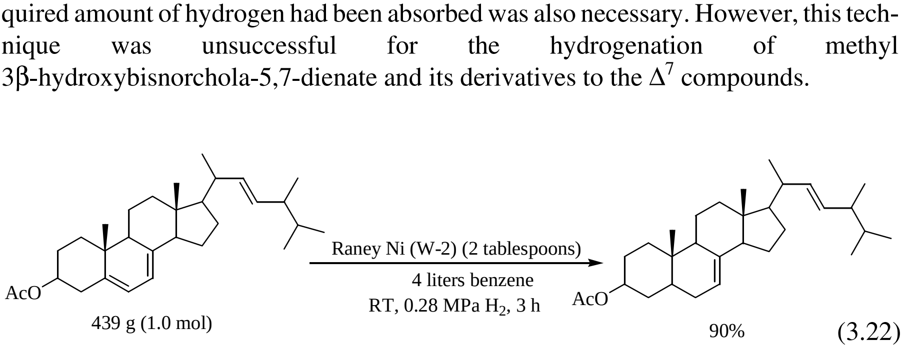
[b]Data of Higashijima, M.; Hó, S.-M.; Nishimura, S. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 2960. Reprinted with permission from Chemical Society of Japan.

[c]A colloidal palladium obtained by reducing palladium chloride with methanol in the presence of poly (N-vinyl-2-pyrrolidone) and sodium hydroxide. Cyclooctadienes (25 mmol·dm^{-3}) were hydrogenated over the colloidal palladium (0.01 mmol·dm^{-3} for 1,3-; 0.02 mmol·dm^{-3} for 1,4-; 0.1 mmol·dm^{-3} for 1,5-cyclooctadiene) in 20 ml of methanol at 30°C and atmospheric pressure. The yields were those obtained when an equimolar amount of hydrogen had been consumed.

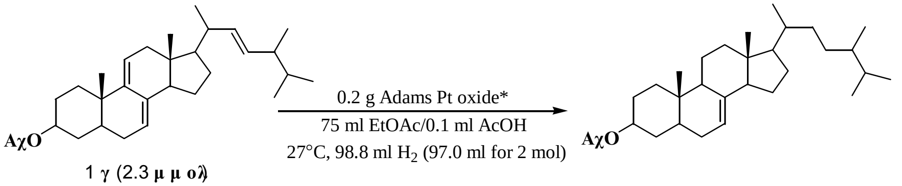
[d]Cyclooctadienes (50 μl) were hydrogenated over 2.0 mg of Pd catalyst in 1.6 ml of tetrahydrofuran at 25°C and atmospheric pressure. The yields were those at the maximum. PAA-poisoned Pd:Pd black poisoned with phenylacetaldehyde; CO-poisoned Pd: Pd black poisoned with carbon monoxide; Pd: Pd black prepared by hydrogen reduction of Pd hydroxide.

[e]The yield was 94.2% with a commercial 5% Pd–C under the conditions in footnote *c*.

was successfully hydrogenated under these conditions. Further hydrogenation of the ergostadiene did not occur readily under these conditions, although ergosterol acetate was converted into 3β-acetoxy-7-ergostene by hydrogenation with Raney Ni in ethyl acetate for 20 h (see eq. 3.10).[67] Laubach and Brunings hydrogenated ergosterol (39.7 g, 0.1 mol) with Raney Ni (W-2, 50 g) in dioxane (800 ml) at room temperature and 0.17–0.20 MPa H_2 and obtained 5-dihydroergosterol quantitatively.[134] Isomerization of 5α-Δ^7-steroids to $\Delta^{8(14)}$ derivatives over platinum oxide may be depressed under neutral[44] or nearly neutral conditions. Thus, 3β-hydroxyergosta-7,22-diene and 3β-acetoxyergosta-7,9(11),22-triene (eq. 3.23) were hydrogenated successfully to the corresponding 7-enes over platinum oxide in ethyl acetate containing a small amount of acetic acid.[135] Separation of the steroid from the catalyst immediately after the required amount of hydrogen had been absorbed was also necessary. However, this technique was unsuccessful for the hydrogenation of methyl 3β-hydroxybisnorchola-5,7-dienate and its derivatives to the Δ^7 compounds.



(3.22)



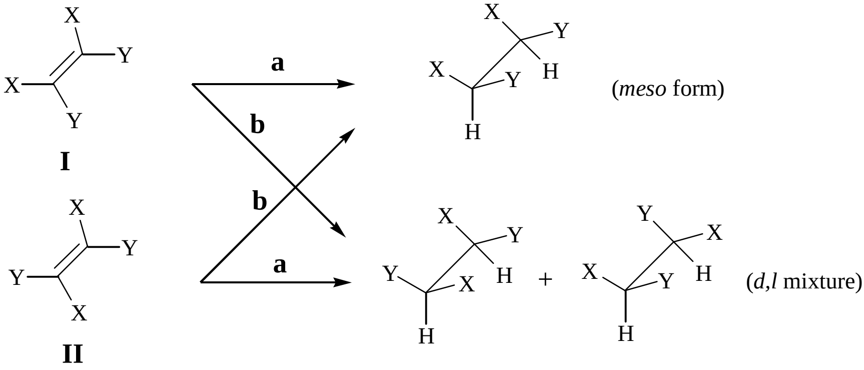
*Prereduced in the solvent. (3.23)

3.7 STEREOCHEMISTRY OF THE HYDROGENATION OF CARBON–CARBON DOUBLE BONDS

3.7.1 *Syn* and Apparent *Anti* Addition of Hydrogen

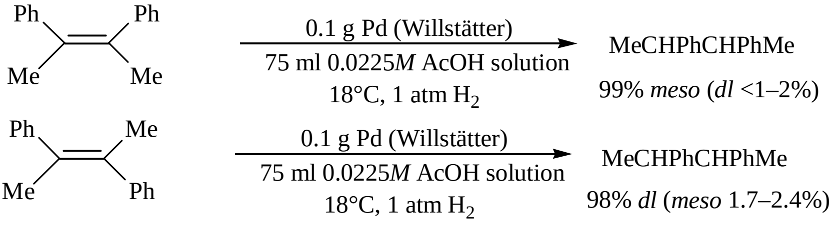
With a few exceptions it has been generally accepted that two atoms of hydrogen are added *syn* to a carbon–carbon double bond from the catalyst surface. If such were the case, *cis*-tetrasubstituted ethylene I would give *meso* form and *trans*-tetrasubstituted ethylene II a racemic mixture, while the situations would be reversed if *anti* addition were the case (Scheme 3.17). The situation is also the same for disubstituted cycloalkenes. *Syn* addition of hydrogen gives the *cis* isomer (*meso* form) and *anti* addition the *trans* isomer (*d,l* mixture). Actually, the mode of hydrogen addition is not so simple and depends on the catalyst, the substrate as well as the hydrogenation conditions (e.g., temperature and hydrogen pressure).

An excellent example of stereospecific *syn* addition is seen in the hydrogenation of *cis*- and *trans*-dimethylstilbene with palladium catalyst (eq. 3.24).[13] Under the same conditions, diethylstilbestrol (**50**, R = H) and its dimethyl ether (**50**, R = Me) were hydrogenated to the products containing, respectively, 90 and 97% of the corresponding racemic 3,4-diphenylhexane derivatives. *Syn* addition decreased to 86 and 70%, re-

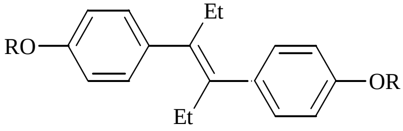


Scheme 3.17 Stereochemistry of the hydrogenation of tetrasubstituted ethylenes. **a**—*syn* addition of H_2; **b**—*anti* addition of H_2.

spectively, with dimethylmaleic acid and dimethylfumaric acid when hydrogenated as their sodium salts over Pd–C in aqueous solution.[12] With a Ni–C catalyst under similar conditions, the *syn* addition product was exclusive with sodium dimethylfumarate and 86% with sodium dimethylmaleate. Dimethylmaleinimide was hydrogenated to nearly pure *meso*-dimethylsuccinimide in the hydrogenation over platinum oxide in ethanol.[136]



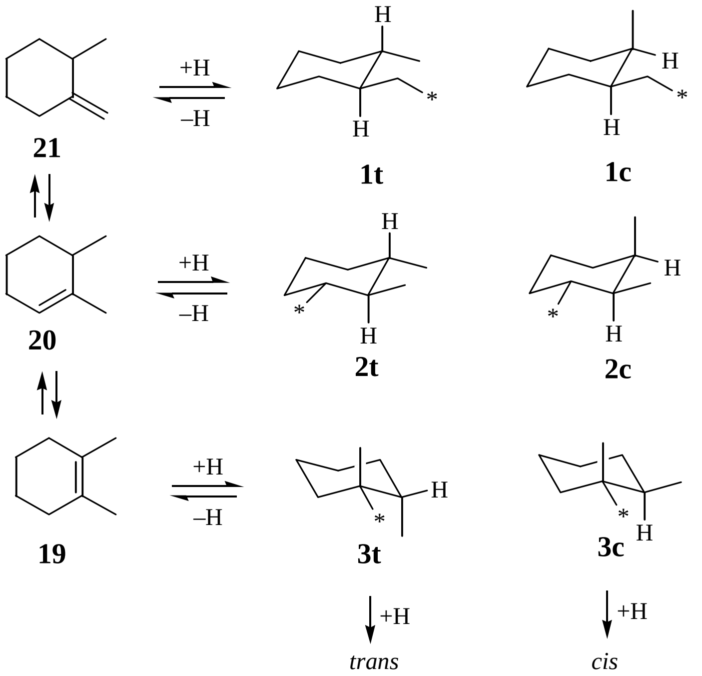
(3.24)



50

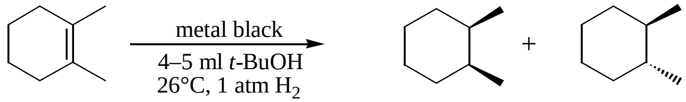
Siegel and Smith found that the hydrogenation of 1,2-dimethylcyclohexene (**19**) with Adams platinum in acetic acid at 25°C and 1 atm H_2 gave a mixture of 81.8% *cis*- and 18.2% of *trans*-1,2-dimethylcyclohexane. The proportion of the *cis* isomer increased to 95.5% under a hydrogen pressure of 30 MPa.[137] In contrast, the hydrogenation of **19** with 5% Pd–Al_2O_3 at 25°C and 1 atm H_2 gave the *trans* isomer predominantly (74.7% *trans* and 25.3% *cis*). Hydrogenation of 1,6-dimethylcyclohexene (**20**) and 2-methylmethylenecyclohexane (**21**) with the palladium catalyst also gave approximately the same composition of the mixture of *cis* and *trans* isomers as that obtained with 1,2-dimethylcyclohexene.[14] The hydrogenations over palladium were accompanied by extensive isomerization and the composition of the reaction mixtures at ~60% hydrogenation was almost the same as with any of the isomeric cyclohexenes as starting material. The results were explained by assuming that the rate-controlling surface reaction is the conversion of the half-hydrogenated states to saturated products where reversal of the half-hydrogenated states to adsorbed olefins as well as desorption of adsorbed olefins are faster than the hydrogenation to give the saturated products. The predominant formation of *trans*-1,2-dimethylcyclohexane over palladium has thus been explained by assuming that the stability sequence among the half-hydrogenated states is **1t** > **1c** >> **2t** > **2c** >> **3c** > **3t** on the basis of decreasing stability of primary > secondary > tertiary half-hydrogenated states and considering their conformations (Scheme 3.18).[14]

Nishimura et al. studied the hydrogenation of **19**–**21** over the six unsupported platinum group metals in *t*-butyl alcohol at 26°C and 1 atm H_2.[138] The hydrogenations of **19** over iridium and osmium have been found to be highly stereoselective, affording



Scheme 3.18 Stereochemistry of the hydrogenation of 1,2- and 1,6-dimethylcyclohexenes and 2-methylmethylenecyclohexane over palladium catalyst.

99.2 and 98.7% yields of *cis*-1,2-dimethylcyclohexane, respectively (eq. 3.25). The order of the platinum metals in the formation of *cis* isomer for **19** (Ir > Os > Ru > Rh > Pt >> Pd) also holds approximately for the hydrogenation of **20** and **21** (Table 3.14). Iridium and osmium are always among the metals that give the highest yields of the *cis* isomer, and palladium always gives the *trans* isomer predominantly. In most cases ruthenium, rhodium, and platinum show the intermediate stereoselectivity between these extreme metals. In general, the tendency of the platinum metals for the formation of the *cis* isomer has been found to correlate inversely with their ability for isomerizing **20** to **19** or **21** to **19** and **20** (see Table 3.14).



(3.25)

0.1–0.15 ml

Catalyst (mg)		
Ir (20)	99.2%	0.8%
Os (7.5)	98.7	1.3
Ru (10)	93.5	6.5
Rh (7.5)	87.6	12.4
Pt (10)	79.1	20.9
Pd (40)	26.4	73.6

TABLE 3.14 The Stereoselectivity and Isomerization Ability of the Platinum Metals in the Hydrogenation of 1,6-Dimethylcyclohexene and 2-Methylmethylenecyclohexane[a,b]

	Proportion of *cis* Isomer in Saturate (%)		Proportion of Isomerized Product (%)[c]	
Catalyst	**20**	**21**	**20** → **19**	**21** → **19** + **20**
Ir	89.0	85.4	0.8	0.0
Os	87.0	84.4	1.1	0.1
Pt	80.6	65.5	2.5	0.27
Ru	86.9	65.5	2.6	2.0
Rh	78.5	63.8	2.7	2.6
Pd	28.9	30.8	44.1	69.0

[a]Data of Nishimura, S.; Sakamoto, H.; Ozawa, T. *Chem. Lett.* **1973**, 855. Reprinted with permission from Chemical Society of Japan.
[b]**20**: 1,6-dimethylcyclohexene; **21**: 2-methylmethylenecyclohexane; **19**: 1,2-dimethylcyclohexene. For the reaction conditions, see eq. 3.25. The amounts of catalyst were reduced for the more reactive substrate **21**.
[c]Given by mol% **19** or **19** and **20** in the product, respectively. The values were obtained at initial stages of hydrogenation.

Weitkamp studied the deuteration of $\Delta^{9,10}$-octalin over carbon-supported platinum metals in cyclohexane at 25°C and 2.45–2.72 MPa D_2.[139] The formation of *cis*-decalin decreased in the following order (proportions in parentheses): 5% Ir–C (97.8 %) > 5% Ru–C (94.7%) > 5% Rh–C (84.9%) > 5% Pt–C (66.6%) > 5% Pd–C (15.6%).

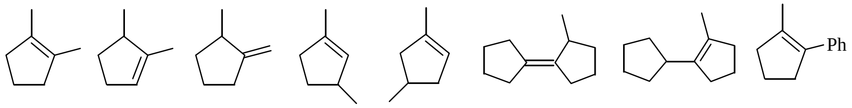
In contrast to 1,2-dimethylcyclohexene, methyl cyclohexene-1,2-dicarboxylate was reported to yield only the *cis* saturated product in the hydrogenation over platinum oxide in acetic acid at 26–27°C, independently of the pressure of hydrogen (0.1–20 MPa) and the concentration of the substrate (0.05–1.0*M*).[140] Hydrogenation of methyl cyclohexene-1,6-dicarboxylate also gave the same result at about 1 atm H_2, but some of the *trans* isomer (6±2%) was formed at a pressure of 13 MPa H_2.

Siegel et al. studied the effects of hydrogen pressure and the structure of the *exo* olefinic groups on the stereochemistry of hydrogenation of 1-alkylidene-4-*t*-butylcyclohexanes over platinum oxide in acetic acid.[141,142] In contrast to the case with 4-*t*-butyl-1-methylcyclohexene, the percent *cis* isomer of the product from 4-*t*-buty-1-methylenecyclohexane decreased with increasing hydrogen pressure from 87% at 0.025 MPa H_2 to 61% at 30 MPa. With respect to the structure of 1-alkylidene groups, the percent *cis* isomer decreased in the order 87% for 1-methylene-, 32% for 1-ethylidene-, and 21% for 1-isopropylidene-4-*t*-butylcyclohexane at low hydrogen pressure. In all the cases the formation of *cis* isomer decreased at high hydrogen pressure, compared with the corresponding values at low pressure. The results have been discussed on the basis of the increasing intramolecular nonbonded interactions from methylene to isopropylidene groups. Kamiyama et al. extended the studies to the hydrogenations over group VIII transition metals other than platinum.[143] The similar effects of the *exo* alkene groups on the *cis/trans* isomer ratios of saturated products were observed for all the catalysts investigated. The results by Siegel et al. and by Kamiyama et al. are summarized in Table 3.15.

TABLE 3.15 Percent *Cis* Isomer from Hydrogenation of 1-Alkylidene-4-*t*-butylcyclohexane[a]

		4-*t*-Butylcyclohexane						
		1-Methylene-		1-Ethylidene-		1-Isopropylidene-		
		H_2 pressure (MPa)						
Catalyst	Solvent	0.1	10	0.1	10	0.1	10	Ref.
Pt	AcOH	87	61	32	17	21	11	142
	Cyclohexane	68	66	26	20	2	4	143
	EtOH	74	70	22	35	5	7	143
Ru	Cyclohexane	87	85	72	66	46	50	143
	EtOH	92	85	66	72	46	55	143
Rh	Cyclohexane	84	78	68	60	34	36	143
	EtOH	90	85	64	69	34	35	143
Pd	Cyclohexane	59[b]	72[b]	26[b]	35[b]	t[b]	t[b]	143
	EtOH	36[b]	47[b]	17[b]	30[b]	t[b]	3[b]	143
Os	Cyclohexane	91	88	86	80	80	74	143
	EtOH	87	84	85	86	78	78	143
Ir	Cyclohexane	84	80	70	74	37	12	143
	EtOH	87	85	65	70	42	16	143
Co	Cyclohexane	33	46	25	44	NR[c]	24	143
Raney Co	Cyclohexane	—	—	30	45	11	15	143
	EtOH	32	47	—	—	—	—	143
Ni	Cyclohexane	47	47	33[b]	33[b]	8[b]	10	143
Raney Ni	Cyclohexane	—	—	21[b]	22[b]	1	4	143
	EtOH	46	47	—	—	—	—	143

[a]Hydrogenations at room temperature.
[b]The products contained large amounts (14–76%) of isomerized cyclohexenes. Over the other metals, the amounts of isomerized product in the reaction mixture were rather small (mostly less than 7%).
[c]No reaction.



51 **52** **53** **54** **55** **56** **57** **58**

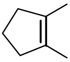
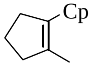
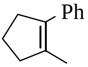
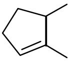
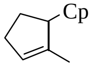
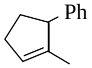
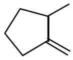
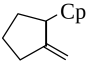
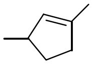
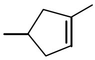
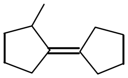
Siegel and Dmuchovsky also studied the stereochemistry of the hydrogenation of isomeric dimethylcyclopentenes and 2-methylmethylenecyclopentane (**51**–**55**) over platinum and palladium catalysts.[144] The hydrogenation of 1,2-(**51**) and 1,5-dimethylcyclopentene (**52**) over reduced platinum oxide in AcOH at 25°C and 1 atm H_2 gives mixtures of *cis*- and *trans*-1,2-dimethylcyclopentanes in which the *trans* isomer is slightly more abundant than the *cis* isomer. Formation of the *cis* isomer from **51** increased from 43% at 0.1 MPa H_2 to 69% at 8.1 MPa H_2 but was almost independent of hydrogen pressure in the case of **52**. Compared to the cyclohexene analogs, the relative rate of isomerization (**52** to **51**) to hydrogenation was greater in the five-membered ring than in the six-membered ring. The isomerization of **51** to **52** was also much

more extensive than in the cyclohexene analogs. These results, together with the fact that **51** and **52** yield almost the same *cis/trans* ratios of 1,2-dimethylcyclopentane at low hydrogen pressures, suggested that the majority of the *trans* isomer formed in the hydrogenation of **51** resulted via prior isomerization to **52**.[145] The greater amount of *trans* saturated isomer formation from **52** than from the corresponding cyclohexene analog **20** at all hydrogen pressures has been explained by the increasing vicinal methyl interactions that accompany the changing geometry of the adsorbed molecule along the reaction path leading to *cis*-1,2-dimethylcyclopentane. Such interactions are expected to disappear in the hydrogenation of 1,3- and 1,4-dimethylcyclopentenes (**54** and **55**), both of which gave *cis*-1,3-dimethylcyclopentane in more than 90% proportions.[144] The hydrogenation of 2-alkylmethylenecyclopentanes over platinum yields the products in which the *cis* isomers predominate. Hydrogenation of 2-methylcyclopentylidenecyclopentane (**56**) over platinum oxide in AcOH gives more *trans*- than *cis*-2-methyl-1-cyclopentylcyclopentane (*trans/cis* = 77:23) at 1 atm H_2. The *trans*:*cis* isomer ratio increased to 79:21 at 8 MPa H_2. Hydrogenation of 2-methyl-1-cyclopentycyclopentene (**57**), an isomerization product of **56**, gave more amounts of the *cis* product, which increased with increasing hydrogen pressure.[146] From these results Siegel and Cozort suggested that the repulsive interactions between 2,2′ and 5,5′ ring positions in the transition state leading to the *cis* isomer become more important than the catalyst hindrance of the 2-methyl group at the species leading to the *trans* isomer, which might reduce at the transition state.[146] As in the cases of the six-membered cycloalkenes, extensive isomerization and predominant formation of the more stable isomers resulted over palladium catalyst, as observed in the hydrogenations of **53**, **56**, and **57**.[144,145] Mitsui et al. investigated the stereochemistry of the hydrogenation of 2-alkylmethylenecyclopentanes and 1,2- and 1,5-disubstituted cyclopentenes over Raney Ni as well as over platinum, palladium, and rhodium, mostly in ethanol as the solvent at room temperature and atmospheric pressure.[147,148] In contrast to the cases with platinum and palladium, the hydrogenation of 1,2-disubstituted cyclopentenes over Raney Ni and Rh–C gave preferentially the *cis* saturated products, whereas the hydrogenation of 1,5-disubstituted cyclopentenes yielded the *trans* products in excess over all the catalysts investigated. Hydrogenation of 1-methyl-2-phenylcyclopentene (**58**) is characteristic in that the *cis* product was formed in high stereoselectivity (> 92%), irrespective of the kind of catalyst. The results by Siegel et al. and by Mitsui et al. on substituted cyclopentene and cyclopentane derivatives are summarized in Table 3.16.

3.7.2 Catalyst Hindrance

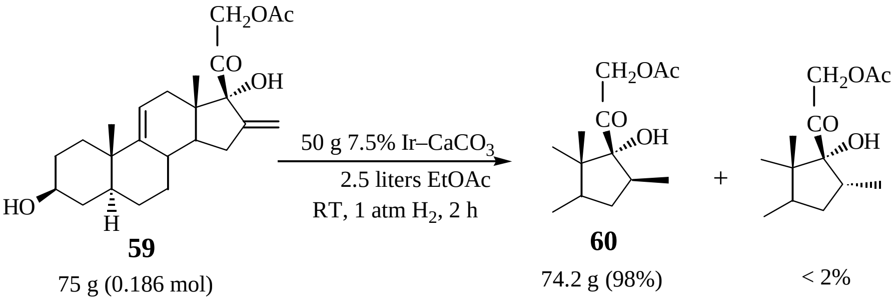
It has been generally accepted that the orientation of adsorption of an unsaturated molecule onto the catalyst is controlled by a steric interaction or hindrance between the substrate and the catalyst; in other words, the adsorption at a less hindered side of the substrate is more favored.[149] The stereochemical outcomes of many hydrogenations have thus been explained by *syn* addition of hydrogen (from the catalyst) to the substrate at a less hindered side. Unless isomerization or some other opposing factors are concerned, such a theory may be successfully applied to those cases where the adsorption of substrate or the formation of half-hydrogenated state is the key step that

TABLE 3.16 Percent *Cis* Isomer in Saturated Product from Hydrogenation of Disubstituted Cyclopentenes and Related Cyclopentylidenes[a,b,c,d,e]

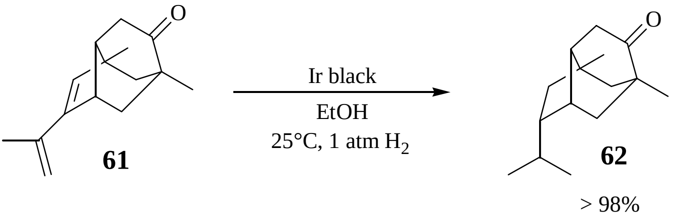
Compound	Catalyst			
	PtO_2	5% Pd–C	5% Rh–C	Raney Ni
	43; 67 (23 MPa) (A) 44 (A); 31 (E)	— 20 (E)	— 82 (E)	— 72,[f] 73[g] (E)
	46; 62 (8 MPa) (A) 42 (A); 17 (E)	32 (0.025 MPa) (A) 14 (A); 13 (E)	94 (13.4 MPa) (A) 80 (E)	— 73,[f] 75[g] (E)
	— 93 (A); 92 (E)	— 98 (A); 99 (E)	— 98 (E)	— 100[f] (E)
	44; 37 (29 MPa) (A) 22 (E)	— 21 (E)	— 42 (E)	— 30,[f] 35[g] (E)
	27; 20 (8 MPa) (A) 21 (E)	— 13 (E)	— 42 (E)	— 17,[f] 17[g] (E)
	— 42 (A); 41 (E)	— 73 (A); 90 (E)	— 66 (E)	— 46[f] (E)
	81; 72 (21 MPa) (A) 75 (E)	21 (A) 33 (E)	— —	— 45,[h] 50[i]
	— 71 (E)	— 15 (E)	— —	— 26,[h] 24[i] (E)
	92 (A) —	— —	— —	— —
	91; 88 (21 MPa) (A) —	— —	— —	— —
	23; 21 (8 MPa) (A) —	10; 13 (13.3 MPa) (A) —	45 (13.4 MPa) (A) —	— —

[a]Data of Siegel, S.; Dmuchovsky, B *J. Am. Chem. Soc.* **1964**, *86*, 2192. Reprinted with permission from American Chemical Society.
[b]Data of Siegel, S.; Cozort, J. R. *J. Org. Chem.* **1975**, *40*, 3594. Reprinted with permission from American Chemical Society.
[c]Data of Mitsui, S.; Saito, H.; Sekiguchi, S.; Kumagai, Y.; Senda, Y. *Tetrahedron* **1972**, *28*, 4751. Reprinted with permission from Elsevier Science.
[d]Data of Mitsui, S.; Senda, Y.; Suzuki, H.; Sekiguchi, S.; Kumagai, Y. *Tetrahedron* **1973**, *29*, 3341. Reprinted with permission from Elsevier Science.
[e]The data on the upper line in each cell are those by Siegel and co-workers obtained at 25°C (27°C for 2-methylcyclopentylidenecyclopentane and related compounds); the data on the lower line in each cell are those by Mitsui and co-workers obtained at room temperature. Unless indicated in parentheses, the compound was hydrogenated at 1 atm H_2 in AcOH (A) or in EtOH (E).
[f]Freshly prepared.
[g]Aged 7 days.
[h]Aged 1 day.
[i]Aged 2–4 weeks.

controls the hydrogenation stereochemistry.[137] Usually, the stereoselectivity of an olefin hydrogenation may be higher over the catalysts of low isomerization ability such as osmium and iridium. As seen from the examples shown in Table 3.14, the formation of *cis* isomer in the hydrogenation of 1,6-dimethylcyclohexene and 2-methylmethylenecyclohexane over the platinum metals increases with decreasing isomerization activity of catalysts. Excellent examples of the stereoselective synthesis using iridium catalysts are seen in the hydrogenation of the 16-methylene steroid **59** to the 16β derivative **60** (eq. 3.26)[150] and in the hydrogenation of the unsaturated ketone **61** to the saturated ketone **62** (eq. 3.27), which was an important step in the total synthesis of (±)-9-isocyanopupukeanane.[151] Both the hydrogenations gave mixtures of stereoisomers with other metals, except in the case of **59** over platinum.



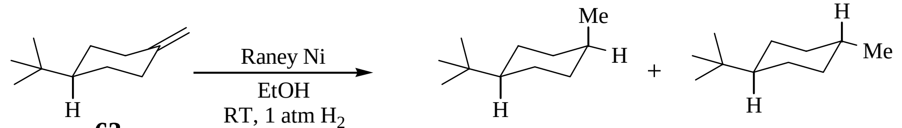
(3.26)



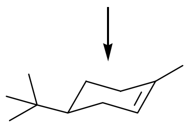
(3.27)

Mitsui et al.[152,153] and Tyman and Wilkins[154] found that different stereochemistries of hydrogenation resulted between freshly prepared Raney Ni and the Raney Ni stored in ethanol or methanol in the hydrogenation of alkylmethylcyclohexenes and alkylmethylenecyclohexanes. Imaizumi et al. investigated this phenomenon in detail in the hydrogenation of 1-*t*-butyl-4-methylenecyclohexane (**63**), where the difference was most pronounced probably because of a fixed conformation of **63**.[155] Thus, the stereoselectivity in the formation of the *cis* isomer increased from a 23% with a fresh catalyst to 95% with the catalyst aged in ethanol for 40 days (eq. 3.28). The isomerization to 4-*t*-butyl-1-methylcyclohexene (**64**) decreased from 11% over the fresh catalyst to only 1% with the aged catalyst. Similar high stereoselectivity and low degree of isomerization to **64** were also obtained with the catalyst that had been refluxed in ethanol or methanol, while the formation of the *trans* isomer predominated with the catalysts aged in water or cyclohexane, and also with those refluxed in 2-propanol, 2-methyl-2-propanol, tetrahydrofuran, and cyclohexane. Since a highly stereoselective

formation of the *cis* isomer was also obtained over a fresh catalyst that had been treated with carbon monoxide (eq. 3.28), the high stereoselectivity of the Raney Ni stored in ethanol was attributed to the modification of the catalyst by the carbon monoxide abstracted from the ethanol used for the storage of the catalyst, rather than the partial surface oxidation of the catalyst. No appreciable change in stereoselectivity was observed in the hydrogenation of **64** with the modified Raney Ni nor in the hydrogenation of **63** with the modified Raney Co. It is noted that in the presence of butylamine the formation of *trans* isomer from hydrogenation of **63** was as much as 51% with Raney Ni and 83% with Raney Co; nevertheless, no isomerization to **64** was observed in either case.



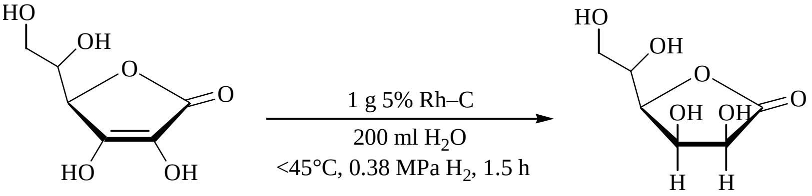
63



Raney Ni		
Freshly prepared	23%	77%
Stored 40 days in EtOH	95	5
Treated with CO	98	2

64 (3.28)

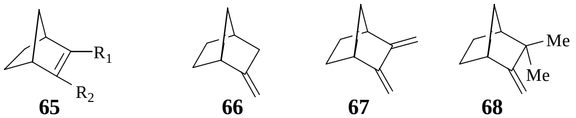
Hydrogenation of L-ascorbic acid (vitamin C) takes place stereoselctively to give L-gluco-1,4-lactone in high yield over Pd–C,[156] or better, over Rh–C in water at temperature below 45°C and 0.38 MPa H_2 (eq. 3.29).[157] It is noted that hydrogen adds preferentially from the least hindered side opposite the side chain.



10.0 g (0.057 mol) 75–90% (3.29)

The hydrogenation of 2,3-disubstituted bicyclo[2.2.1]hept-2-enes (norbornenes) (**65**) over platinum catalysts generally leads to *endo–cis* derivatives, indicating preferential *syn* addition of hydrogen from the *exo* side.[158,159] Thus, the hydrogenation of bicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylic acid and its dimethyl ester in acetic acid or methanol gave the corresponding *endo–cis* products in high yields via fast uptake of first mole of hydrogen to give the 2-norbornene derivatives followed by slow hydrogen uptake of second mole of hydrogen to give the *endo–cis* products. The formation of the *endo–trans* product was ~5%, and no *exo* product was found in the case of the

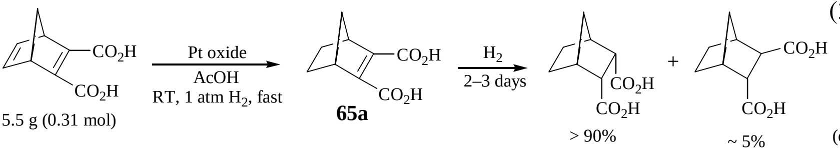
free acid **65a** (eq. 3.30). Similar results were also obtained in the hydrogenation of bicyclo[2.2.1]hept-2-ene-2-carboxylic acid with colloidal platinum (Skita) in HCl–AcOH and Adams platinum in AcOH or in MeOH, as well as in slightly alkaline solution of colloidal palladium (Paal). The hydrogenation of 2-methylenenorbornane (**66**),[158] 2,3-dimethylenenorbornane (**67**)[159] and 3,3-dimethyl-2-methylenenorbornane (camphene) (**68**)[160] also leads to the products resulting from the *exo* or *exo–cis* addition of hydrogen.



65 **66** **67** **68**

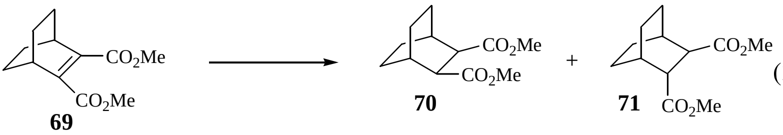
a: $R_1 = R_2 = CO_2H$
b: $R_1 = R_2 = CO_2Me$
c: $R_1 = H$; $R_2 = CO_2H$
d: $R_1 = R_2 = Me$

(3.30)



(eq3.30)

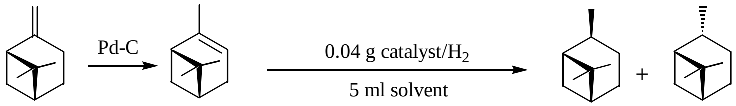
In contrast to the case with **65a**, the hydrogenation of dimethyl bicyclo[2.2.2]oct-2-ene-2,3-dicarboxylate (**69**) yields the *syn-endo*-addition product **70** over Rh–C and Pt–C in heptane at 25°C and 1 atm H_2 (eq. 3.31).[161,162] The hydrogenation over Pt–C, however, was accompanied by 7.1% of apparent *anti*-addition product **71**. The presence of small amounts of a strong acid, which had little effect on the hydrogenation with rhodium, greatly increased the formation of **71** over Pd–C, which amounted to as much as 60% in the presence of *p*-TsOH in methanol.



(3.31)

The addition of hydrogen to β- and α-pinenes (**72** and **73**) takes place preferentially from the methylene bridge side, rather than from the isopropylidene bridge side, as might be expected from the consideration of catalyst hindrance. Van Tamelene and Timmons obtained a 84:16 *cis*:*trans* mixture in the hydrogenation of **72** over platinum at unspecified conditions.[160] The stereoselectivity for the *cis* isomer is even higher with **73**; more than 90% yields of *cis*-pinane were obtained with platinum catalysts.[160,163]

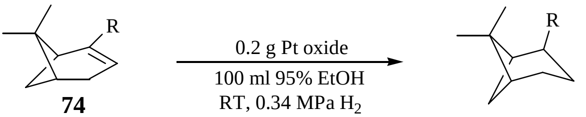
cis-Pinane was also the predominant product in the hydrogenation with Raney Ni in ether at elevated temperature and pressure (up to 107°C and 10.3 MPa).[164] The hydrogenation of **72** over Pd–C is accompanied by rapid and complete isomerization to **73** from which the *cis* isomer is formed in greater amounts than the *trans* isomer. By choosing appropriate conditions, Cocker et al. obtained *cis*-pinane in over 98% yield with 5% Pt–C in ethanol and *trans*-pinane in more than 50% yields over 5% Pd–C in propionic acid at elevated temperatures (eq. 3.32).[163] Eigenmann and Arnold obtained the *cis*-dihydro products in high yields in the hydrogenation of α-pinene derivatives **74** with platinum oxide in acetic acid or ethanol at room temperature and low hydrogen pressure.[165] In the cases of myrtenic acid (**74**, R = CO_2H) and myrtenol (**74**, R = CH_2OH) (eq. 3.33), the corresponding *cis*-dihydro derivatives were obtained in 89 and 92% yields, respectively.[165]



(3.32)

72 **73** 0.2 g

Catalyst	T (°C)	P (MPa)	Solvent	*Cis*	*Trans*
5% Pt–C	20	10	EtOH	98.5	1.5
5% Pt–C	20	0.1	EtOH	90.0	10.0
PtO_2	20	0.1	EtOH	93.5	6.5
5% Pd–C	20	0.1	EtOH	65.0	35.0
5% Pd–C	20	0.1	$EtCO_2H$	74.0	26.0
5% Pd–C	127	0.1	$EtCO_2H$	47.0	53.0



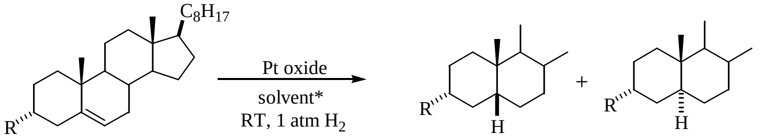
(3.33)

74

20 g (0.13 mol)
(R = CH_2OH)

18.6 g (92%)

There have been known many examples that the hydrogenation of 3β-substituted Δ^5-steroids yields mainly or exclusively saturated steroids of 5α series.[166] Lewis and Shoppee studied the influence of various 3α substituents on the stereochemical course of the hydrogenation of Δ^5-steroids, and found that the 3α substituents lead to the preferential and sometimes exclusive formation of 5β-cholestane derivatives.[166] The hydrogenations over platinum oxide were effectuated in methanol or ethyl acetate in the presence of traces of strong acids such as perchloric acid, sulfuric acid or hydrobromic acid. The results summarized by Lewis and Shoppee (eq. 3.34), which also include those by Haworth et al.,[167] suggest that the bulkier the axial 3α substituent, the larger is the proportion of 5β steroid formed. The hydrogenation of Δ^4-steroids usually leads to a mixture of 5α and 5β compounds and the stereochemical influence of 3α and 3β substituents is less marked than in the cases of Δ^5-steroids.[168]



(3.34)

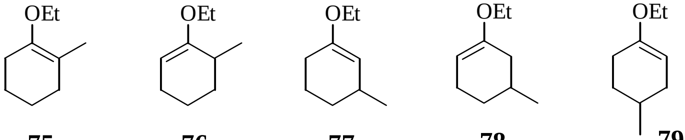
* Mostly with a trace amount of HBr or $HClO_4$.

R		
OH	~50	~40
OMe	>90	
OAc	>90	
Cl	>90	
Br	~40 (+ ~60% 5β-cholestane)	
NHMe	~100	
NHAc	>90	
NMe_2	~100	

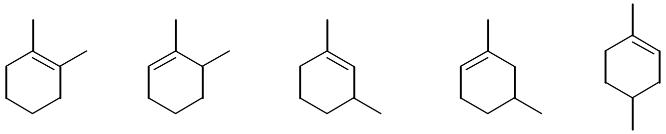
3.7.3 Effects of Polar Groups

Polar groups attached directly to or located apart from a carbon–carbon double bond may have a marked effect on the stereochemical outcome of the hydrogenation of the carbon–carbon double bond.

The hydrogenation of methyl-substituted 1-ethoxycyclohexenes **75**–**79** over palladium catalyst affords predominantly less stable saturated ethers (Scheme 3.19).[15,170,171] As described previously, the hydrogenation of the corresponding dimethylcyclohexenes over palladium always leads to predominant formation of more stable isomers, the proportions of which are also shown in Scheme 3.19 for comparison. Since extensive isomerization occurs prior to hydrogenation, isomeric ethoxycyclohexenes **75** and **76**, **77** and **78**, as well as the corresponding dimethylcyclohexenes afford nearly the same results between the isomer pairs even at rather initial stages of



75	**76**	**77**	**78**	**79**
97.8,[a] 93.5[a,b]	96.0,[a] 92.0[a,b]	20.6[a]	15.3[a]	90.9, 81.9[b]

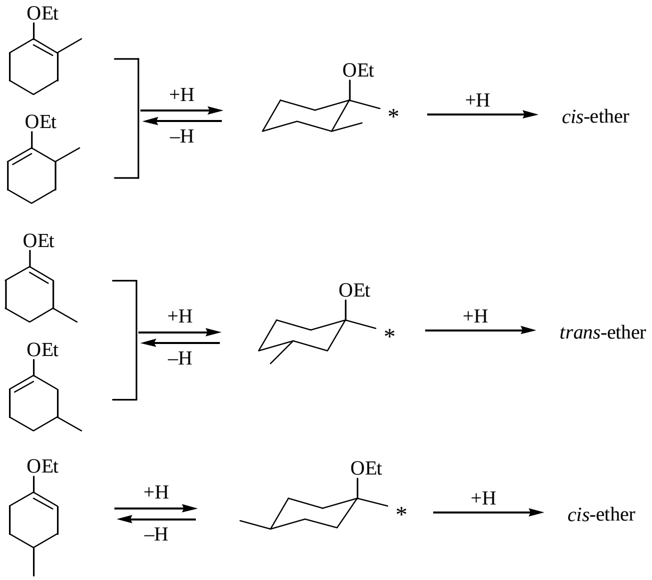


26.4[b]	28.9[b]	83.9[a]	80.8[a]	27,[c] 28[d]

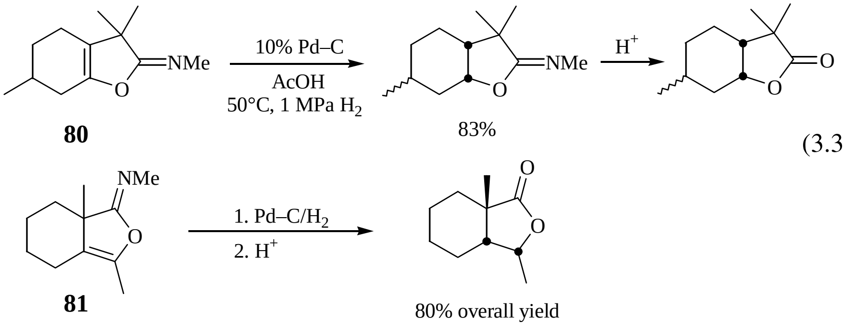
Scheme 3.19 Percent *cis* isomers from hydrogenation of methyl-substituted 1-ethoxycyclohexenes and the corresponding dimethylcyclohexenes over Pd black in ethanol at 25°C and 1 atm H_2 ([a]the values obtained at initial stages of hydrogenation; [b]in *t*-BuOH at 25 or 26°C; [c]10% Pd–C at room temperature[153]; [d]5% Pd–C in AcOH[15]).

hydrogenation. The differences in the stereochemistry of hydrogenation between these enol ethers and the corresponding dimethylcyclohexenes as observed over palladium are in most cases much smaller over the other platinum metals. The similarity in the stereochemistry of hydrogenation between these two groups of compounds are seen in hydrogenations over osmium and iridium. Thus, the *cis/trans* isomer ratios of the saturated product from hydrogenation of **77** and **78** were 12 and 0.89 over osmium, compared to 12 and 0.80 with the corresponding dimethylcyclohexenes, and 9.0 and 0.72 over iridium, compared to 8.2 and 0.73 with the corresponding dimethylcyclohexenes.[170] The predominant formation of less stable stereoisomers in the hydrogenation of enol ethers **75–79** over palladium has been explained on the basis of the preferential addition of first hydrogen to the β-carbon atom to give the half-hydrogenated states adsorbed at the α carbon, namely, the carbon bearing the ethoxyl group. If the product-controlling step over palladium is the formation of saturated ethers, as in the hydrogenation of dimethylcyclohexenes,[14] the predominant half-hydrogenated species from **75–79** on the catalyst surface are expected to be those to give the less stable saturated ethers on hydrogenation, as shown in Scheme 3.20 (compare with Scheme 3.18).

The β,γ double bonds of *N*-substituted enoliminolactones **80** and **81** are hydrogenated in high yields and high stereoselectivities over Pd–C to give the saturated *cis*-iminolactones, subsequent hydrolysis of which afforded the corresponding *cis*-fused bicyclic γ-butyrolactones in high overall yields (eq. 3.35).[172] It is noted that the enol lactone obtained by hydrolysis of **80** was resistant to hydrogenation under the same conditions.

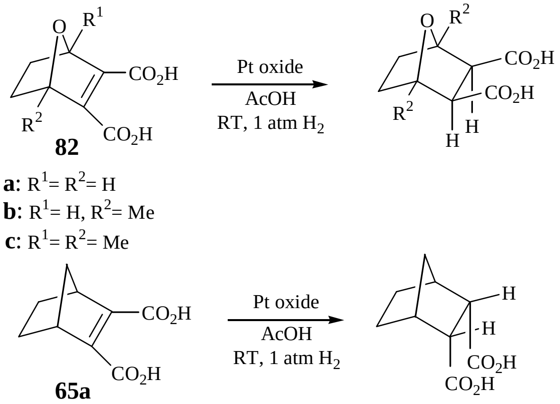


Scheme 3.20 Predominant formation of the less stable isomers of saturated ethers in the hydrogenation of methyl-substituted 1-ethoxycyclohexenes over palladium.



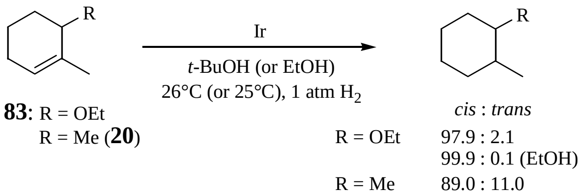
(3.35)

An oxygen group located apart from a carbon–carbon double bond in a molecule may have a marked effect on the stereochemistry of the hydrogenation of the C–C unsaturation. Usually, the oxygen group favors the addition of hydrogen from the face remote from the oxygen. A classic example is the hydrogenation of 7-oxabicyclo[2.2.1]hept-2-ene-2,3-dicarboxylic acids (**82**).[173] The hydrogenation of **82** over platinum oxide in acetic acid affords preferentially the *exo–cis* products, while the *endo–cis* product was formed in more than 90% from the corresponding bicyclo[2.2.1]heptene derivative **65a** (eq. 3.36; see also eq. 3.30).



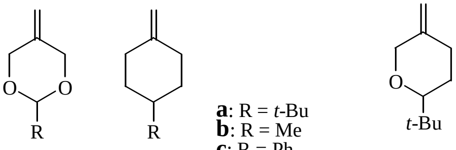
(3.36)

The hydrogenation of 1-methyl-6-ethoxycyclohexene (**83**, R = OEt) over iridium catalyst gave the corresponding saturated ether of a high *cis/trans* ratio. The stereoselectivity to the *cis* isomer is much higher in **83** than in the corresponding dimethyl analog **20** (eq. 3.37).[138] Although the predominant formation of the *cis* isomers with both **83** and **20** appears to be related to a quasiaxial conformation of the allylic substituents,[174,175] it would be difficult to explain the much higher stereoselectivity in **83** than in **20** by the steric requirement of the allylic ethoxyl group alone. Thus, the results indicate that the allylic ethoxyl group in **83** increases markedly the addition of hydrogen from the side away from the ethoxyl group for a reason other than the steric effect.



(3.37)

The hydrogenation of 2-substituted 5-methylene-1,3-dioxanes (**84a**–**c**) over 5% Pt–C in methyl acetate, ethyl acetate, or chloroform as well as with platinum oxide in methanol afforded the corresponding saturated products consisting of 93–95% of the *cis* isomers and 5–7% of the *trans* isomers.[176] The proportions of the *cis* isomers were considerably larger than those expected in the hydrogenation of the corresponding 4-alkylmethylenecyclohexanes (83 and 74% *cis* in the cases of **85a**[141] and **85b**[4] with platinum oxide in acetic acid, respectively). The effect of the allylic ring oxygen on the stereochemistry of hydrogenation of the *exo* methylene group has later been investigated in detail by Ishiyama et al. with **84a** and 2-*t*-butyl-5-methylenetetrahydropyran (**86**) over a variety of supported and unsupported group VIII metals in ethanol or cyclohexane at room temperature and atmospheric pressure.[177,178] The results summarized in Table 3.17 show that the proportions of the *cis* products are in all cases greater with **84a** (73–98%) and **86** (75–99%) than with **85a** (14–91%). Differences in the stereoselectivity are particularly marked over cobalt, nickel, and palladium catalysts because the *trans* isomers are usually formed predominantly with **85** over these catalysts. The effect of the allylic ring oxygen to increase the formation of the *cis* isomers has been explained by an interaction of the nonbonded electrons of the oxygen with the π orbital of the alkenic bond in **84** and **86**, which may favor the adsorption of the compounds at the equatorial side of the methylene group and thus increase the addition of hydrogen from the equatorial side to give the *cis* isomers.



84 **85** **86**

Senda et al. studied the stereochemistry of hydrogenation of 1,6-dimethyl-3-methylenepiperidine (**87**) and 1,2-dimethyl-4-methylenepiperidine (**88**) over group VIII transition metals in ethanol at room temperature and atmospheric hydrogen pressure.[179] In the case of **87**, the hydrogen addition took place preferably from the equatorial side except over palladium and Raney Ni, and with **88** the hydrogen addition from the axial side predominated over all the catalysts investigated. The results have been compared with those of the corresponding carbocyclic analogs, and the stereochemical outcomes have been discussed on the basis of an intramolcular interaction between the nitrogen lone pair and the unsaturated bond.

TABLE 3.17 Percent *Cis* Isomer from Hydrogenation of 2-Alkyl-5-methylene-1,3-dioxanes, 2-*t*-Butyl-5-methylenetetrahydropyran, and the Corresponding Methylenecyclohexanes[a,b]

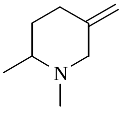
		Compound Hydrogenated[c]				
Catalyst	Solvent	**84a**	**85a**	**84b**	**85b**	**86**
Raney Fe	EtOH	95	56	88	53	—
	Cyclohexane	95	56	—	—	—
Raney Co	EtOH	80	35	73	37	—
	Cyclohexane	73	26	—	—	75
Co	Cyclohexane	75[d]	46[d]	—	—	95[d]
Raney Ni	EtOH	89	43	89	45	—
	Cyclohexane	98	14	—	—	93
Ni	Cyclohexane	90	29	—	—	93
Ru–C	EtOH	87	84	88	77	—
Ru	Cyclohexane	89	87	—	—	98
Rh–C	EtOH	92	69	87	61	—
Rh	Cyclohexane	89	84	—	—	94
Pd–C	EtOH	97	24	90	26	—
Pd	Cyclohexane	87	59	—	—	99
Os–C	EtOH	90	84	88	62	—
Os	Cyclohexane	90	91	—	—	94
Ir–C	EtOH	82	70	76	66	—
Ir	Cyclohexane	91	84	—	—	96
Pt–C	EtOH	88	54	84	64	—
Pt oxide	EtOH	98	71	98	64	—
Pt	EtOH	98	69	95	62	—
	Cyclohexane	91	68	—	—	97

[a]Data of Ishiyama, J.; Senda, Y.; Imaizumi, S. *J. Chem. Soc., Perkin Trans. 2* **1982**, 71 (hydrogenations in ethanol at room temperature and atmospheric pressure). Reprinted with permission from Royal Society of Chemistry.

[b]Data of Ishiyama, J.; Kamiyama, S.; Senda, Y.; Imaizumi, S. *Chem. Ind.* (*Lond.*) **1988**, 466 (hydrogenations in cyclohexane at room temperature and atmospheric pressure). Reprinted with permission from Society of Chemical Industry.

[c]**84a**, 2-*t*-butyl-5-methylene-1,3-dioxane; **85a**, 4-*t*-butyl-1-methylenecyclohexane; **84b**, 2-methyl-5-methylene-1,3-dioxane; **85b**, 4-methyl-1-methylenecyclohexane; **86**, 2-*t*-butyl-5-methylenetetrahydropyran.

[d]Hydrogenated at 9.8 MPa H_2.



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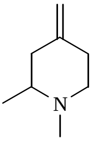
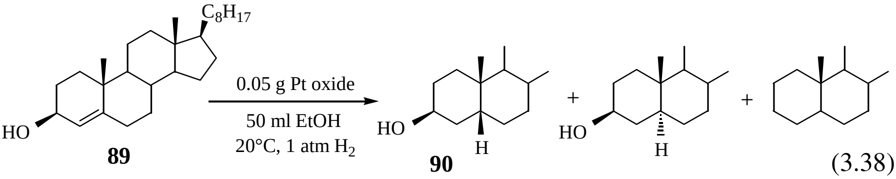


88

The hydroxyl group in an olefinic compound may favor the addition of hydrogen to the olefinic bond from the side of the hydroxyl group, as observed in hydrogenations over an alkaline platinum or Raney Ni catalysts. Dart and Henbest showed that in the hydrogenation of 4-cholesten-3β-ol (**89**) over Adams platinum in ethanol the formation of 5β-cholestan-3β-ol (**90**), the product added *cis* to the hydroxyl group, was increased by the presence of small amounts of alkaline sodium salts such as sodium nitrate (reduced to nitrite), nitrite, cyanide, or sodium hydroxide, mainly at the expense of hydrogenolysis to give hydrocarbons.[180] The 5β-ol **90**: hydrocarbon ratio was also influenced by the ratio of chloroplatinic acid to sodium nitrate and the fusion temperature employed for the preparation of Adams platinum oxide. When Adams platinum oxide was prereduced and washed with water to remove alkaline substances,[181] the yield of **90** fell to below 20% and the yield of hydrocarbon increased correspondingly (eq. 3.38). Since the hydrogenation of 4-cholestene in ethanol over Adams platinum under an alkaline condition (sodium nitrite) afforded 55% of 5β-cholestane and 45% of 5α-cholestane, the results indicated that the 3β-hydroxyl group increased the β addition of hydrogen from 55% to ~70%. In contrast, the α-addition of hydrogen increased from 45 to 60% in the hydrogenation of the methyl ether of **89**.



89 **90**

(3.38)

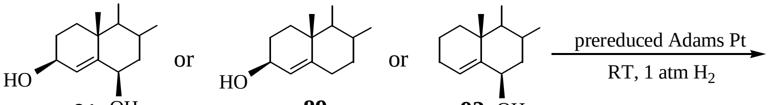
0.542 g (1.4 mmol)

Catalyst	Composition of Product (%)		
1. Prepared at 400°C (1:10)*	8	19	73
2. Prepared at 420°C (1:20)*	71	20	9
3. As 2, but prereduced and washed	11	15	74
4. As 3 + $NaNO_2$†	65	32	3
5. As 3 + NaCN†	63	30	7
6. As 3 + NaOH†	63	36	1
7. Prepared at 420°C (1:50)*	70	24	6
8. As 7, but prereduced and washed	19	22	59

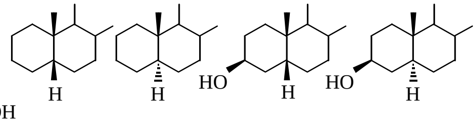
* The relative weights of hexachloroplatinic acid to sodium nitrate used for fusion.
† Each (1 wt% of Pt oxide) was added dissolved in a drop of water.

4-Cholestene-3β,6β-diol (**91**) is hydrogenated quantitatively to 5β-cholestane-3β,6β-diol over Adams platinum oxide in ethanol.[182] However, when the platinum oxide was reduced in the presence of the substrate or prereduced insufficiently, the hydrogenation often proceeded rapidly to completion to give largely the hydrogenolysis products of mostly 5α series.[183] The hydrogenation of **91** in acetic acid or in the presence of strong acid was similarly accompanied by extensive hydrogenolysis.[184,185] Detailed studies by GC analysis on the hydrogenation of **89**, **91**, and 4-cholesten-6β-ol (**92**) (eq. 3.39) have shown that the 6β-hydroxyl group is much more responsible for the β addition of hydrogen than the 3β-hydroxyl group in the hydrogenation in ethanol over sufficiently prereduced platinum oxide, while the 6β-hydroxyl group is more readily susceptible to hydrogenolysis than the 3β-hydroxyl in the hydrogenation in acetic

acid.[186] The differences between the 3β- and 6β-hydroxyl groups toward the directive effect and the hydrogenolysis have been considered to reflect the fact that the 3β-hydroxyl group exists in a quasiequatorial conformation and the 6β-hydroxyl group in an axial conformation. The occurrence of hydrogenolysis over insufficiently reduced platinum oxide probably comes from the circumstances that Adams platinum oxide is contaminated with alkaline substances such as amorphous sodium platinate or sodium platinum bronze formed during the fusion procedure using sodium nitrate.[181,187] It is probable that platinum oxide is reduced with hydrogen to active platinum first at the part that is not contaminated with the alkaline substances. The parts of platinum oxide rich in alkaline substances are then reduced more slowly to an active form.[187,188] The platinum surface having no alkaline substance may become strongly acidic with ionized adsorbed hydrogen[189,190] and thus catalyzes efficiently the hydrogenolysis of the allylic hydroxyl group. When Adams platinum oxide has been prereduced sufficiently with hydrogen, the platinum surface produced may become sufficiently alkaline to depress the hydrogenolysis and can adsorb the hydroxyl group strongly.

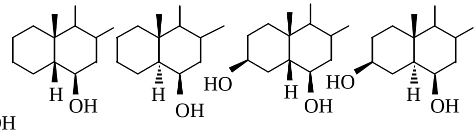


91 **89** **92**



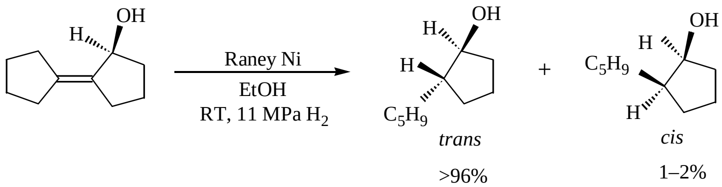
In EtOH				
91			1%	2%
89	1%	2%	76%	21%
92				
In AcOH				
91	4%	40%	3%	28%
89	7%	47%	14%	32%
92	11%	60%		

(3.39)



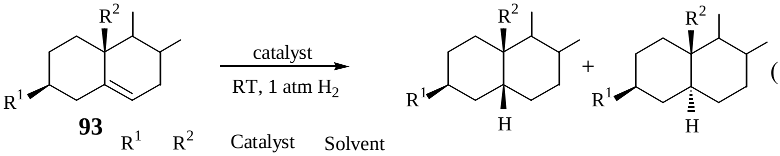
In EtOH				
91			97%	
89				
92	93%	7%		
In AcOH				
91	1%	3%	15%	6%
89				
92	16%	13%		

Howard observed the directive effect of a hydroxyl group in the hydrogenation of 2-cyclopentylidenecyclopentanol in ethanol over Raney Ni at room temperature and 11 MPa H_2; the product was at least 96% *trans*-2-cyclopentylcyclopentanol and a trace (1–2%) of a lower-boiling component, the *cis*-alcohol (eq. 3.40).[191] The hydrogenation over other metals, nickel boride (P-1), Ru–C, platinum oxide, Rh–C, and Pd–C, also gave predominantly the *trans*-cyclopentanol (81–92%).[192] The high stereoselectivity to *trans*-cyclopentanols over Raney Ni was also obtained with 2-isopropylidenecyclopentanol (97%)[192] and 2-butylidenecyclopentanol (91–96%),[193] and to a lesser extent with 2-butylidenecycloheptanol (74%).[193] As would be expected, the main product (50–66%) over palladium in the latter two alcohols was 2-butylcycloalkanones formed by isomerization. The sequence in increasing percentage of the *cis* alcohol Ni < Ru < Pt < Rh < Pd was suggested to reflect the isomerizing ability of the catalysts rather than a decreasing affinity of the catalysts for adsorption through the hydroxyl group. However, from the results on the hydrogenation of 2-cyclopentylidene-1-methylcyclopentanol, 3-methyl-2-cyclopentenol and 3-methyl-2-cyclohexenol, Mitsui et al. interpreted the findings to indicate that the hydrogenations over Raney Ni were directed by the hydroxyl group to increase the addition of hydrogen from the side of the hydroxyl group, but such an effect of the hydroxyl group did not appear to be operative in the hydrogenations over Pd–C where half of the products was hydrocarbons and the more stable isomers were formed predominantly.[194]



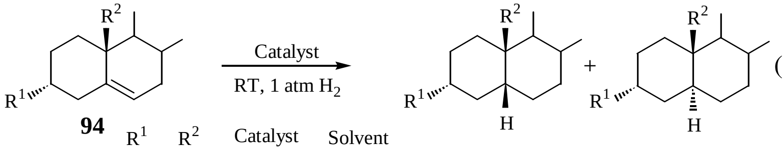
(3.40)

Similar directive effects of the hydroxyl group were also observed in the hydrogenation of 19-hydroxy Δ^5-steroids **93** (eq. 3.41) and **94** (eq. 3.42) over platinum and rhodium catalysts[195,196] and with a tetrahydrofluorene derivative **95** over Pd–C (eq. 3.43).[197,198] It is noteworthy that the stereoselectivity for formation of the 5β compounds is especially high in the hydrogenation of 3α-acetoxy-19-hydroxy and 3α,19-dihydroxy compounds in **94** with rhodium and not much different between the values obtained in isopropyl alcohol and in acetic acid as the solvent. These results do not appear surprising in view of the condition that the catalyst employed in isopropyl alcohol was a rhodium black containing practically no alkaline substances. Thompson found that a large directive effect of the hydroxymethyl group located at the 9a position of the compound **95**. Hydrogenation of **95**, R = CH_2OH over 5% Pd–C in 2-methoxyethanol at room temperature and atmospheric pressure gave a *cis/trans* product ratio of 95:5, while the methoxycarbonyl compound **95**, R = CO_2Me gave a ratio of 15:85 (eq. 3.43).[197] This great difference in the stereochemistry of hydrogenation has been interpreted in terms of attractive (haptophilic) versus repulsive (steric) interactions between the catalyst surface and the 9a angular group. Among the functional R groups investigated, the product added *cis* to R was the greatest with R = CH_2OH and decreased in the following order (percent *cis* in parentheses): CH_2OH (95) > CHO



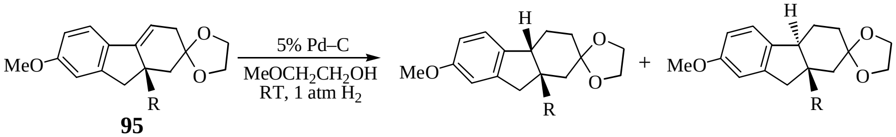
93 (3.41)

R^1	R^2	Catalyst	Solvent		
AcO	Me	Pt	AcOH	10.6%	88.4%
AcO	Me	Rh	EtOH	3	91.4
AcO	CH_2OH	Pt	AcOH	36.5	59
AcO	CH_2OH	Rh	AcOH	32.0	58.3
AcO	CH_2OH	Rh	EtOH	57.5	34.5
HO	Me	Rh	AcOH, *i*-PrOH	~0	~100
HO	CH_2OH	Rh	AcOH	27	73
HO	CH_2OH	Rh	*i*-PrOH	24	76



94 (3.42)

R^1	R^2	Catalyst	Solvent		
AcO	Me	Pt	AcOH	79%	21%
AcO	Me	Rh	AcOH	82	18
AcO	Me	Rh	*i*-PrOH	81	19
AcO	CH_2OH	Pt	AcOH	97	3
AcO	CH_2OH	Rh	AcOH	>99	0
AcO	CH_2OH	Rh	*i*-PrOH	>99	0
HO	Me	Pt	AcOH	63	37
HO	Me	Rh	AcOH	62	38
HO	Me	Rh	*i*-PrOH	46	54
HO	CH_2OH	Pt	AcOH	90	10
HO	CH_2OH	Rh	AcOH	98	2
HO	CH_2OH	Rh	*i*-PrOH	90	10



95 (3.43)

R = CH_2OH	95%	5%
R = CO_2Me	15	85

(93) > CN (75) > CH=NOH (65) > CO_2Na (55) > CO_2Li (23) > CO_2H (18) > CO_2Me (15) > COMe (14) > $CONH_2$ (10). The results, however, could not be correlated with any single one of the steric or electronic measures.[198]

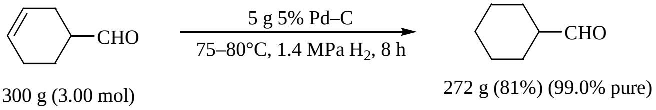
3.8 SELECTIVE HYDROGENATIONS IN THE PRESENCE OF OTHER FUNCTIONAL GROUPS

3.8.1 Isolated Double Bonds in the Presence of a Carbonyl Group

Isolated double bonds are usually hydrogenated in preference to a carbonyl group over most catalysts, unless the double bonds are strongly hindered. Palladium catalysts ap-

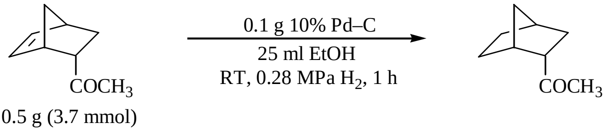
pear to be best for obtaining saturated carbonyl compounds selectively in view of their low activity toward the carbonyl function, although platinum and nickel catalysts are also applicable to the preparation of saturated aldehydes and ketones with care to avoid overhydrogenation. On the other hand, over copper–chromium oxide 3-cyclohexenecarboxaldehyde was selectively hydrogenated to the corresponding unsaturated alcohol (see eq. 5.21). Citronellal with a trisubstituted double bond was hydrogenated selectively at the aldehyde group to give citronellol, an unsaturated alcohol, over a lead-poisoned ruthenium (see eq. 5.22) or chromium-promoted Raney Ni.

3-Cyclohexene-1-carboxaldehyde was hydrogenated to the corresponding saturated aldehyde in high yield using a small amount of 5% Pd–C at a temperature of 75–80°C and 1.4 MPa hydrogen pressure without solvent (eq. 3.44).[199] The hydrogenation had to be performed in a reaction vessel with good agitation and below 80°C in order to obtain a satisfactory result. Higher temperatures gave increasingly higher amounts of cyclohexanemethanol. 1,2,5,6-Tetrahydrophthalaldehyde was hydrogenated to the corresponding saturated dialdehyde over Pd–C in methanol at room temperature and atmospheric pressure with only a low yield.[200] Citronellal was hydrogenated to the saturated aldehyde over platinum oxide or Pd–$BaSO_4$,[201] while with Ni–kieselguhr, the aldehyde group was hydrogenated first.[201,202]



(3.44)

A number of examples are known where palladium catalysts were applied to the selective hydrogenation of unsaturated ketones to saturated ketones. Hydrogenation of 4-acetylcyclohexene to acetylcyclohexane took place rapidly with a small amount of Pd–C. Uptake of hydrogen never went beyond 1 molar equivalent.[203] Examples of the selective hydrogenations using palladium catalysts are shown in eqs 3.45,[204] 3.46,[205] and 3.47.[206]



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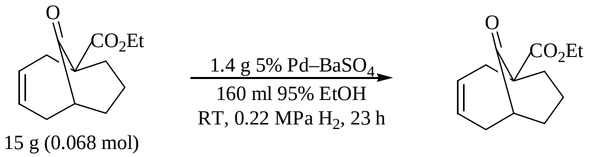
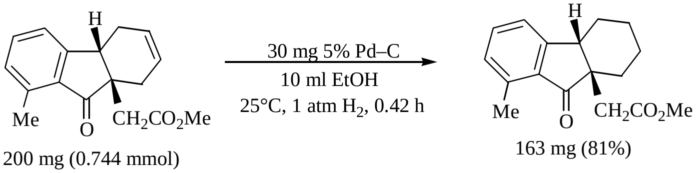
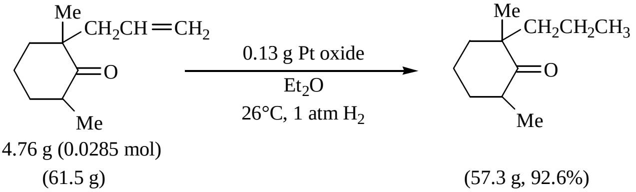


(3.46)

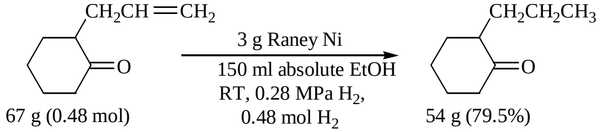


(3.47)

Examples of the use of platinum and nickel catalysts are seen in the hydrogenation of 2-allyl-2,6-dimethylcyclohexanone to 2-propyl-2,6-dimethylcyclohexanone over platinum oxide (eq. 3.48)[207] and 2-allylcyclohexanone to 2-propylcyclohexanone over Raney Ni (eq. 3.49).[208]

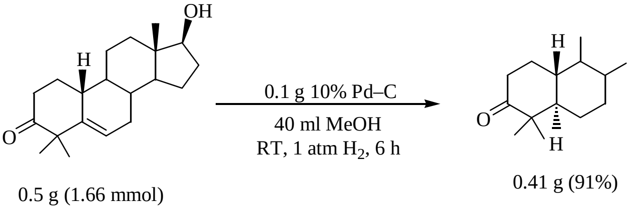


(3.48)

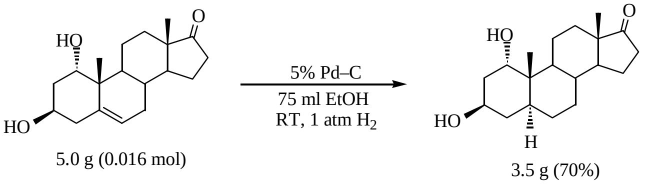


(3.49)

The Δ^5 double bond in steroids, which is seldom hydrogenated over platinum oxide in neutral solvent or Raney Ni, has been hydrogenated selectively in the presence of the oxo groups at C3, C17, or C20 over Pd–C in alcohol (eqs 3.50[209] and 3.51[210]) or platinum oxide in acetic acid (eqs 3.52[211] and 3.53[212]). In the latter cases using platinum oxide in acetic acid, however, some formation of 5β compounds took place. Small amounts of overhydrogenation products were oxidized to the ketones with chromium trioxide.



(3.50)



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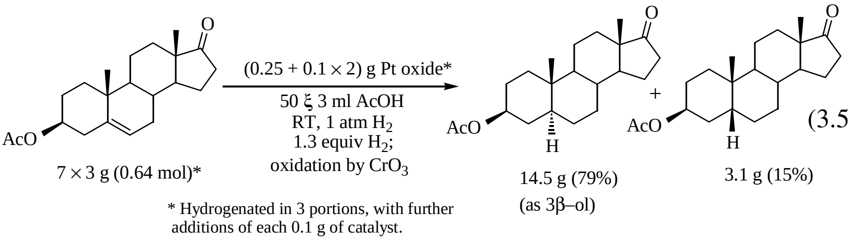

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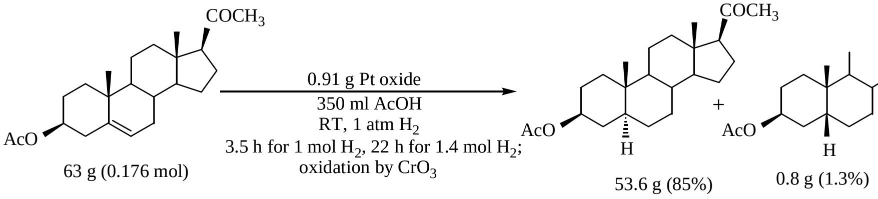
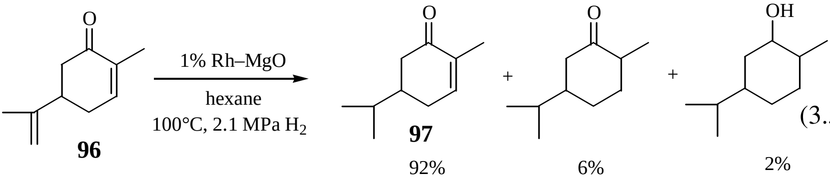


(3.53)

The isopropenyl group can be hydrogenated in preference to an α,β-unsaturated carbonyl group system. Thus, Gomez et al. have shown that carvone (**96**) is selectively hydrogenated to carvotanacetone (**97**) over Rh–MgO in a 92% selectivity in hexane at 100°C and 2.1 MPa H_2, although the degree of conversion has not been indicated (eq. 3.54).[213] The MgO-supported catalyst showed particularly higher selectivity to carvotanacetone than SiO_2- and TiO_2-supported ones.



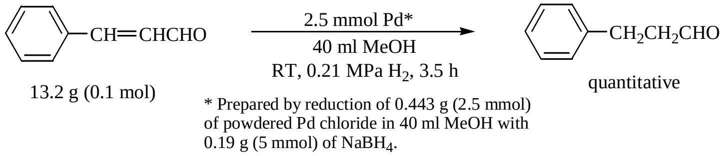
(3.54)

3.8.2 Double Bonds Conjugated with a Carbonyl Group

α,β-Unsaturated aldehydes are selectively hydrogenated over palladium catalysts to give saturated aldehydes. According to Freifelder, overhydrogenation practically did not occur in the hydrogenation of 2-methy-2-pentenal over 5% Pd–C with 2.5% catalyst to substrate at 60°C and 0.3 MPa H_2. With Raney Ni it was necessary to carefully follow hydrogen uptake.[214] Overhydrogenation with Raney Ni was also observed in the hydrogenation of 2,4-pentadienal in water at room temperature and 0.2–0.3 MPa H_2, where pentanal as well as 1-pentanol were obtained.[215] Successful applications of Pd–C catalyst are also seen in the hydrogenation of crotonaldehyde to butyraldehyde[216] and of 4,4-bis(ethoxycarbonyl)cyclohexene-2-carboxaldehyde to the corresponding cyclohexane derivative.[217]

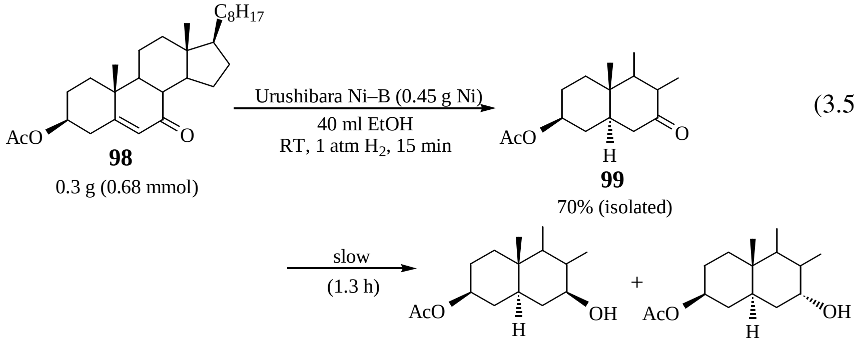
Hydrogenation of cinnamaldehyde to 3-phenylpropionaldehyde over palladium catalyst may be accompanied by the formation of 3-phenyl-1-propanol and propylbenzene,[218] although the formation of 3-phenylpropionaldehyde usually predominates.[219,220] The composition of the products are widely affected by the nature of palladium catalysts, solvents, supports, and additives.[216,221] The hydrogenation over Pd–Al_2O_3 in ethanol or over Pd–kieselguhr in acetic acid gave 3-phenylpropionaldehyde quantitatively at room temperature and atmospheric pressure. The addition of a 1:1 ratio of ferrous chloride to palladium also resulted in quantitative formation of 3-phenylpropionaldehyde in the hydrogenation over 5% Pd–C in methanol.[221] This result was contrasted with those obtained with platinum oxide where iron additives led

to predominant formation of cinnamyl alcohol[222] (see eq. 5.23). According to a patent, formation of the hydrocinnamyl alcohol in the hydrogenation of *p*-*t*-butyl-α-methylcinnamaldehyde (20.2 g) at 100°C and 0.41 MPa H_2 was depressed to only 1.2% with addition of 0.044–0.053 g of potassium acetate to 1.2 g of 5% Pd–Al_2O_3.[223] Over borohydride-reduced palladium, only 3-phenylpropionaldehyde was formed and no other products were detected (eq. 3.55).[224]



(3.55)

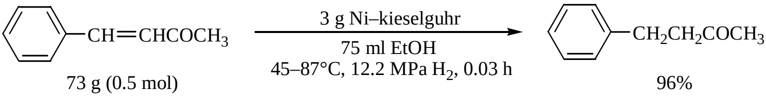
α,β-Unsaturated ketones are hydrogenated more readily to the saturated ketones than in the case of α,β-unsaturated aldehydes because of a lesser trend of the resulting saturated ketones toward overhydrogenation. An isolated carbon–carbon double bond, which is resistant to hydrogenation under mild conditions, may be subject to hydrogenation when the double bond is conjugated with a carbonyl group. For example, the Δ^5 double bond of 7-oxocholestery acetate (**98**) is hydrogenated over Urushibara Ni in ethanol at room temperature and atmospheric pressure to give 7-oxo-5α-cholestanyl acetate (**99**), although usually the Δ^5 double bond is resistant to hydrogenation over nickel catalysts under mild conditions. Further hydrogenation of **99** to 7β- and 7α-hydroxy compounds is rather slow and **99** is obtained in good yield by interrupting the hydrogenation when the hydrogen uptake has slowed down after the absorption of 1 molar equivalent of hydrogen (eq. 3.56).[225]



(3.56)

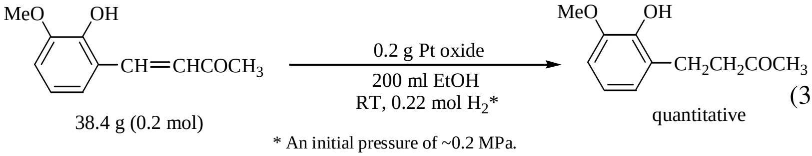
Benzalacetone (eq. 3.57), benzalacetophenone, and mesityl oxide were converted to the corresponding saturated ketones in high yields by hydrogenation over Ni–kieselguhr at relatively low temperatures.[226] Overhydrogenation to alcohol in the hydrogenation of benzalacetone, mesityl oxide, or isophorone (3,5,5-trimethyl-2-cyclohexenone) over Raney Ni could be depressed with addition of metal halides such as KI and BaI_2.[227] The addition of metal halides was also effective in the selective hydrogenation of mesityl oxide over various nickel catalysts in ethanol at elevated tem-

perature and pressure[228] as well as in the vapor-phase hydrogenation over Ni–kieselguhr catalyst.[229]



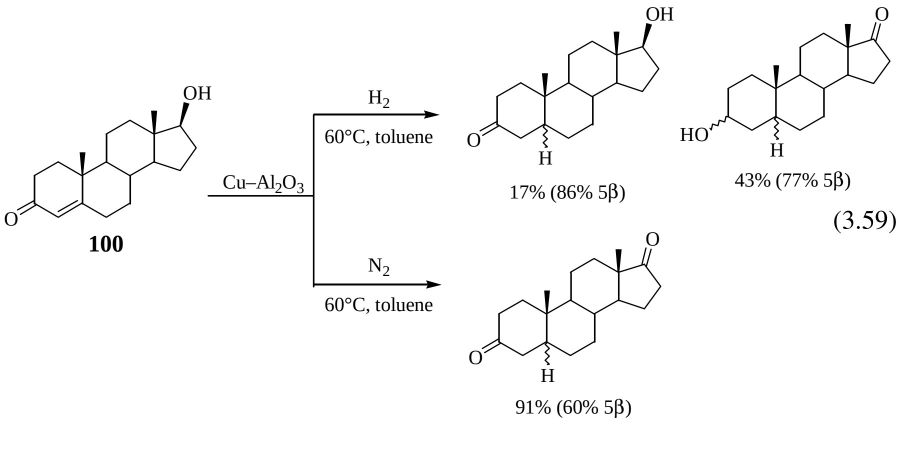
(3.57)

Freifelder hydrogenated 4-(2-hydroxy-3-methoxyphenyl)-3-buten-2-one quantitatively to the corresponding butanone with use of a lower-than-normal amount of platinum oxide (~0.5%) or Raney Ni (~5%) and 105–110% of 1 molar equivalent (1 equiv) of hydrogen in ethanol at room temperature (eq. 3.58).[230] Overhydrogenation took place when 1 wt% of platinum oxide or 10–15 wt% of Raney Ni was used at 0.3 MPa H_2 where a large excess of hydrogen was present. Freifelder suggests that use of a low ratio of Pd–C would also have been satisfactory,[230] although Mannich and Merz found that hydrogenation of the corresponding 4-hydroxy-3-methoxy derivative over Pd–C absorbed 1.5 equiv of hydrogen giving 25.5% of the corresponding 2-butanol together with the butanone as the major product.[231]



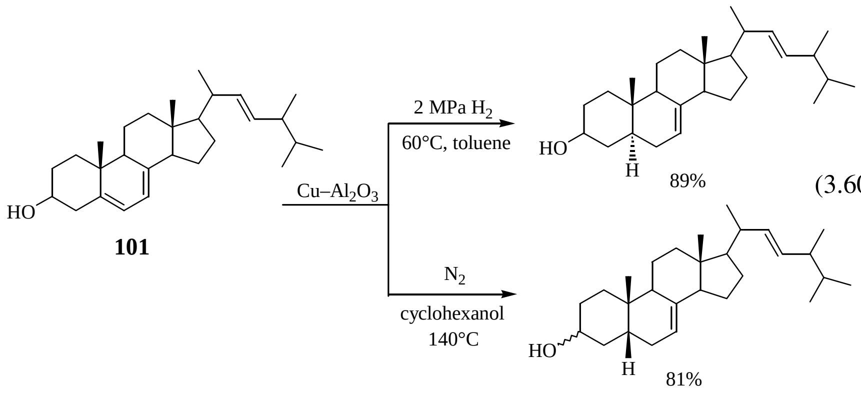
(3.58)

Ravasio et al. found that hydrogenation of testosterone (**100**) in the presence of Cu–Al_2O_3 in toluene proceeded smoothly at 60°C and 0.1 MPa H_2. However, the expected product 17β-hydroxyandrostan-3-one was found in only a minor amount after absorption of 1 equiv of hydrogen. The major products were instead 3-hydroxyandrostan-17-ones, indicating a hydrogen transfer reaction occurring between the 17β-hydroxy and the 3-oxo functional groups.[232] The hydrogen transfer reaction takes place also in the



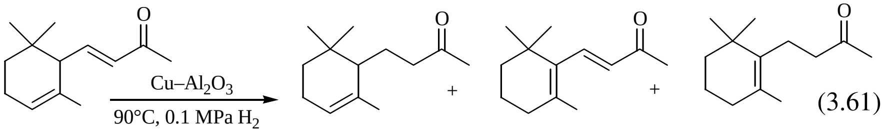
(3.59)

absence of molecular hydrogen. Thus, when testosterone was stirred under the atmosphere of nitrogen at 60°C in the presence of Cu–Al_2O_3, androstane-3,17-dione was obtained in 91% yield (60% 5β)(eq. 3.59). Ergosterol (**101**) with a conjugated diene moiety is selectively hydrogenated at the Δ^5 double bond to give 5α-ergosta-7,22-dien-3β-ol in a high yield of 89% under conditions of high hydrogen availability, whereas in cyclohexanol under nitrogen 5β-ergosta-7,22-dien-3-ol was obtained in 81% yield (eq. 3.60). It would be apparent that the latter product was formed through a 3-oxo-4-ene derivative as intermediate.



(3.60)

The hydrogenation of α-ionone over prereduced Cu–Al_2O_3 in toluene is accompanied by partial isomerization of the unconjugated C–C double bond and gives a mixture of products. The isomerization could be suppressed by using dioxane as the solvent (eq. 3.61), thus suggesting participation of weakly electrophilic Cu(I) surface site or of Al^{3+} acidic sites.[233]

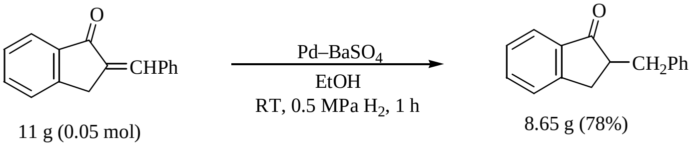


(3.61)

solvent			
toluene	47%	4%	46%
dioxane	83%		

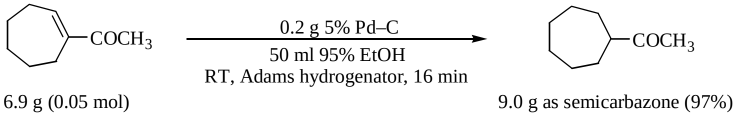
Palladium catalysts have been most widely used for the selective hydrogenation of α,β-unsaturated ketones to saturated ketones because of their high activity for the conjugated carbon–carbon double bond as well as their low activity for the carbonyl group. There is little tendency for overhydrogenation with palladium catalysts except in some special cases such as in aryl ketones, which may be hydrogenated rather readily to benzyl-type alcohols and hydrocarbons over palladium. Even in these cases, the selective hydrogenation has often been achieved successfully by using appropriate palladium catalyst. For example, 2-benzyliden-1-indanone was hydrogenated to the

saturated ketone in methanol over Pd–$BaSO_4$ in a good yield (eq. 3.62)[234] (see also eq. 3.47).



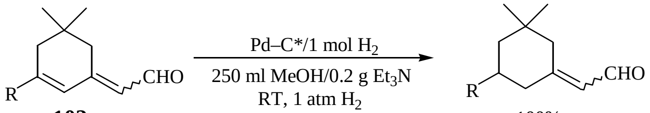
(3.62)

No difficulty exists in the hydrogenations where aliphatic and alicyclic ketones are formed. Thus, acetylcyclohepetene was hydrogenated to acetylcycloheptane in 97% yield over Pd–C (eq. 3.63).[235]



(3.63)

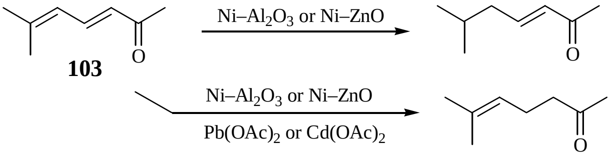
Selective partial hydrogenation of conjugated polyunsaturated aldehydes or ketones may be possible with limited substrates and catalysts or conditions. Traas et al. was successful to selectively hydrogenate the γ,δ double bond of the conjugated dienals **102**, prepared from isophorone, to give the corresponding α,β-unsaturated aldehydes quantitatively over Pd–C poisoned by sulfur and quinoline in methanol in the presence of triethylamine; the hydrogenation was stopped when 1 equiv of hydrogen had been consumed (eq. 3.64).[236]



102
0.1 mol (R = H or Me)

(3.64)

Freidlin et al. found that 6-methyl-3,5-heptadien-2-one (**103**) was hydrogenated to the 3-en-2-one over unmodified Ni–Al_2O_3 and Ni–ZnO by 1,2 addition of hydrogen to the 5,6 double bond, while the 5-en-2-one was formed preferentially in the presence of Pb, $Pb(OAc)_2$ or $Cd(OAc)_2$ (eq. 3.65), by 1,4 addition of hydrogen to the C=C–C=O system, as was presumed from the results on the hydrogenation of **103** in MeOD solution.[237,238]

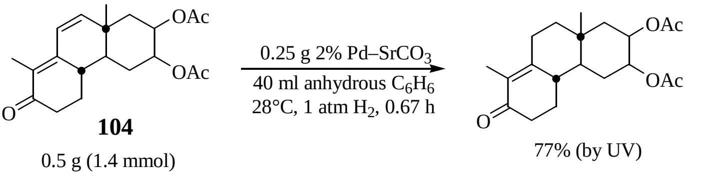


103

(3.65)

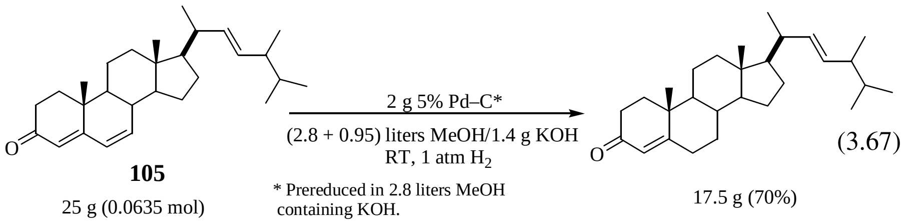
Conjugated cyclic dienone **104** was partially hydrogenated to the corresponding α,β-unsaturated ketone over 2% Pd–$SrCO_3$ in benzene as solvent (eq. 3.66).[239] A similar

partial selective hydrogenation was also achieved quantitatively over 2% Pd–$SrCO_3$ in isopropyl alcohol containing sodium hydroxide.[240]

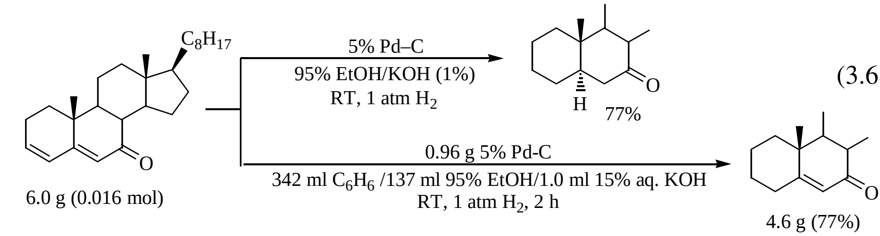


(3.66)

Ergosta-4,6,22-trien-3-one (**105**) was transformed into the 4,22-dien-3-one in the hydrogenation over prereduced 5% Pd–C in methanol containing potassium hydroxide. Optimum selectivity of the hydrogenation system was found to be dependent on the reduction of the catalyst prior to addition of the substrate and on the concentration of the alkali. Uniformly high conversions were obtained in the media of 0.0010–0.010*M* potassium hydroxide. Above and below this concentration range the yields of dienone were somewhat lower. The hydrogenation ceased with uptake of 1.0–1.1 equiv of hydrogen to give the dienone in 70–75% isolated yields (eq. 3.67).[241] Successful use of Pd–C in MeOH–KOH is also seen in a similar hydrogenation.[242] Selective hydrogenation of chloesta-3,5-dien-7-one over 5% Pd–C in the presence of a small amount of potassium hydroxide was dependent on the solvent used.[243] The hydrogenation in ethanol gave the saturated ketone, 5α-cholestan-7-one, in ~80% yield, whereas in ethanol–benzene the enone, cholest-5-en-7-one, was obtained in ~75–80% yield (eq. 3.68).



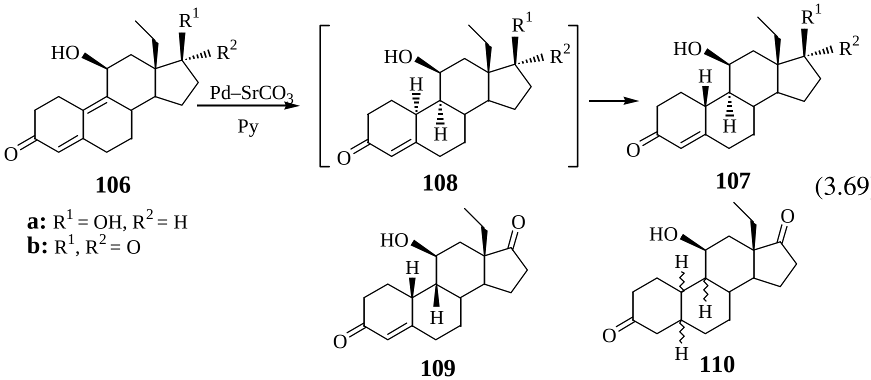
(3.67)



(3.68)

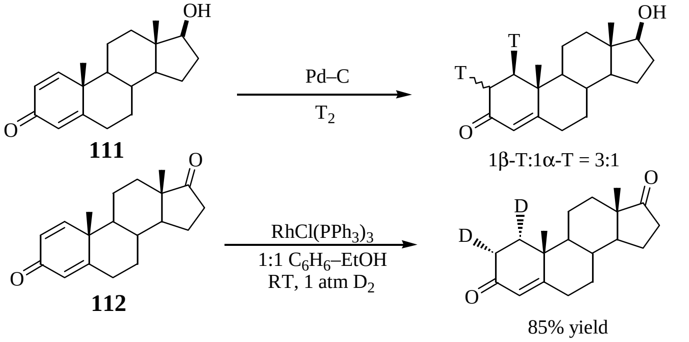
Liu et al. were successful to transform 17-substituted 13β-ethyl-11β-hydroxygona-4,9-dien-3-ones (**106**) into the corresponding 11β-hydroxygon-4-en-3-ones (**107**) in the hydrogenation over Pd–$SrCO_3$ in pyridine (eq. 3.69).[244] The selectivity of Pd–$SrCO_3$ hydrogenation was highly dependent on the 17 substituent. The 17β-hydroxy

compound **106a** gave only the (9α,10β) dihydro product **107a** with a yield of 81%. It has been suggested that the 9α,10β isomer was produced via the initial product 9α,10α isomer **108a** formed by the addition of hydrogen from the opposite side of 17β-hydroxyl. On the other hand, 17-oxo compound **106b** yielded two dihydro products **107b** (9α,10β) and **109** (9β,10β) with the yield of 45% and 4%, respectively, together with a small amount of tetrahydro product **110**.



(3.69)

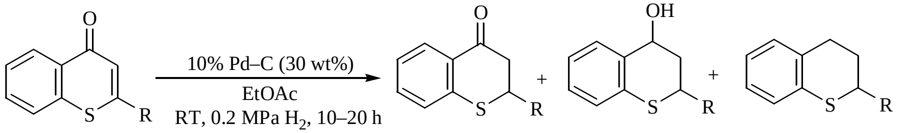
Hydrogenation of $\Delta^{1,4}$-dien-3-one steroids over a heterogeneous catalyst usually does not proceed selectively and gives a mixture of Δ^1- and Δ^4-3-ones in low yields.[245–248] Tritiation or deuteration of 17β-hydroxy-1,4-androstadien-3-one (**111**) over palladium has revealed that the attack at C1 occurs predominantly (~75%) from the β face.[247] By contrast, homogeneous hydrogenation of 1,4-androstadiene-3,17-dione (**112**) with the rhodium–phosphine complex $RhCl(PPh_3)_3$ proceeds very selectively to yield 4-androstene-3,17-dione in high yield and deuterium addition to the 1,2 double bond has proved to take place predominantly from the α face (eq. 3.70).[249] Ravasio and Rossi, however, found that $Cu–Al_2O_3$ showed a high selectivity of 93% in hydrogen addition to the 1,2 double bond in the hydrogenation of **112** in toluene at 60°C and 1 atm, with 74% maximum yield of 4-androstene-3,17-dione.[250]



(3.70)

Kumar et al. were successful to hydrogenate 2-substituted thiochromones (**113**) to thiochromanones (**114**) with use of an excess amount (30 wt%) of 10% Pd–C in ethyl acetate at room temperature, although the chromones with an electron-donating sub-

stituent such as *p*-methoxyphenyl at the 2 position (**113e**) led to complete hydrogenolysis of the carbonyl group to the methylene (eq. 3.71).[251] The reaction of **113** with Zn/AcOH, Li/liquid NH_3, Wilkinson's catalyst, diimide, and cyclohexene/Pd–C failed to give the desired product.

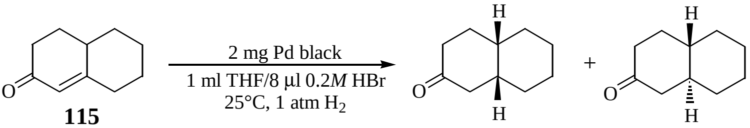


	114			
113				
a: R = Me	65%	0	0	
b: R = Et	62	0	0	
c: R = Ph	45	18	31	
d: R = *p*-ClC_6H_4	10	25	40	
e: R = *p*-$MeOC_6H_4$	0	0	66	

(3.71)

3.8.3 Stereochemistry of the Hydrogenation of $\Delta^{1,9}$-2-Octalone and Related Systems

The stereoselectivity in the hydrogenation of bicyclic and polycyclic α,β-unsaturated ketones with the double bond at the ring juncture has been the subject of extensive investigations.[252] Formation of *cis*-2-decalone in the hydrogenation of $\Delta^{1,9}$-2-octalone (**115**) with palladium catalysts increases with increasing polarity of aprotic solvents and also in the presence of acid, especially in nonhydroxylic solvents.[253,254] Hydrobromic acid has been found to be more effective than hydrochloric acid for *cis*-2-decalone, especially in tetrahydrofuran (eq. 3.72).[255] Formation of alcoholic products was also completely depressed in the presence of hydrobromic acid, although the rate of hydrogenation became considerably lower than in the presence of hydrochloric acid.[256]



115
0.03 g (0.2 mmol)

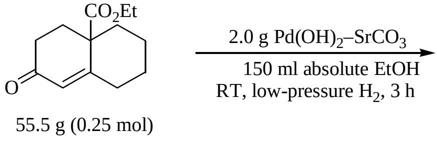
99.5% (98%)* 0.5% (2%)*

(3.72)

* In presence of 8 µl 0.3*M* HCl.

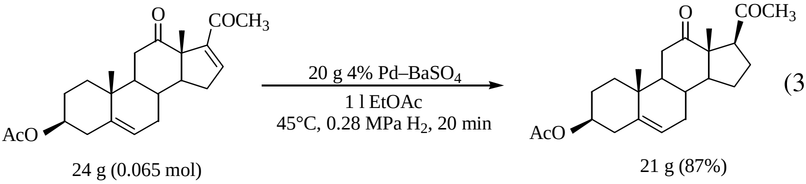
Hydrogenation of $\Delta^{1,9}$-2-octalones with an angular substituent at the C10 carbon over palladium catalyst gives the corresponding *cis*- and *trans*-decalone mixtures, the proportion of which depends on the substituent. When the angular group is CH_3,[239,257] $CHCl_2$,[258] or CH_2OH,[259] the *cis* ring-fused products result predominantly. In contrast, when the angular group is ethoxycarbonyl, the *trans* ring-fused product is formed in high yield (eq. 3.73).[260] The hydrogenation in acetic acid over platinum oxide also led to the compound of the *trans* series, exclusively.[261] With 10-methyl-$\Delta^{1,9}$-2-octalone, however, the effect of acid to increase the formation of *cis*-ketone was found to be

much smaller (75–79% *cis* in THF–HCl) than in the case of **115** (eq. 3.72); rather, a greater selectivity to the *cis* isomer was obtained in the hydrogenation in pyridine (80–84% *cis*), or better, in 4-methoxypyridine (87% *cis*).[256]



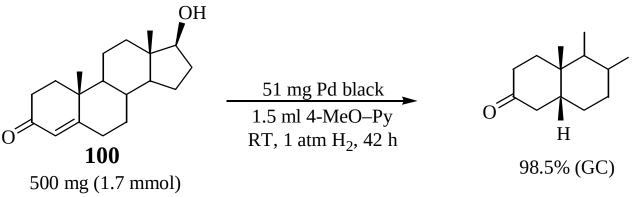
(3.73)

The addition of hydrogen to Δ^{16}-20-one steroids occurs preferentially from the α face to give the 17β-substituted derivatives.[262] As an example, 3β-acetoxypregna-5,16-diene-12,20-dione was hydrogenated to the pregn-5-ene-12,20-dione derivative in high yields over Pd–$BaSO_4$ in ethyl acetate with the 5,6 double bond intact (eq. 3.74).[262a]

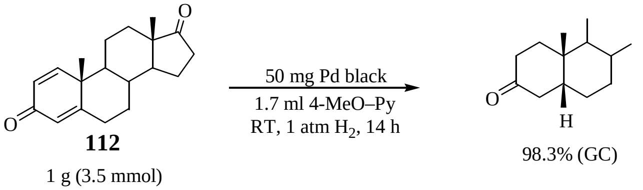


(3.74)

The hydrogenation of a number of 3-oxo-Δ^4-steroids has been investigated with palladium catalysts under various conditions. The formation of 5β-ketones is favored in both alkaline[263] and strongly acidic conditions.[264] The hydrogenation in *N*-methylpyrrolidine,[265] pyridine,[265,266] or better in 4-methoxypyridine,[255] has been found to give high yields of 5β-ketones without formation of any alcoholic products. The use of pyridines is also advantageous in that pyridines are excellent solvents for steroids and hydrogenations can be carried out in a rather concentrated solution. 3-Oxo-$\Delta^{1,4}$-steroids are also hydrogenated to give high yields of 5β-ketones under these conditions.[255] With use of 4-methoxypyridine as solvent, instead of pyridine, most of 3-oxo-Δ^4- and 3-oxo-$\Delta^{1,4}$-steroids are hydrogenated to saturated 5β-ketones in 95–99.9% yields over palladium catalyst. For example, testosterone (**100**) was hydrogenated to the corresponding 5β-ketone in 97.1% yield in 4-methoxypyridine, compared to 90.6% yield in pyridine under the same conditions. Equation 3.75 is an example of the hydrogenation carried out on a larger scale. Similarly, androsta-1,4-diene-3,17-dione (**112**) was hydrogenated to 5β-androstane-3,17-dione in 97.3% yield in 4-methoxypyridine, compared to 88.0% in pyridine. A preparative run is shown in eq. 3.76.

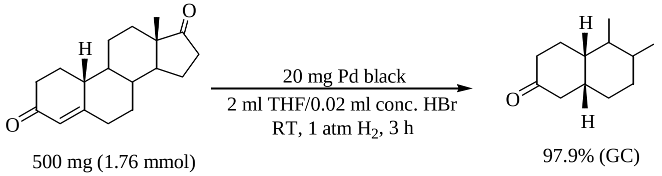


(3.75)



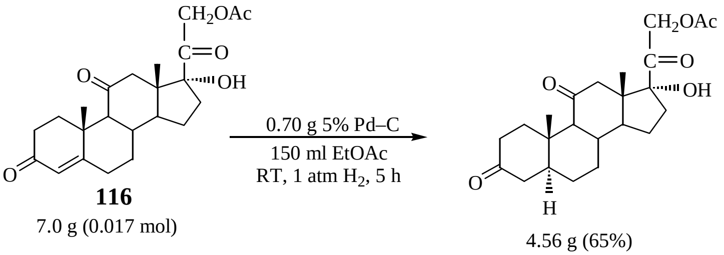
(3.76)

In contrast to the usual steroids with the 10β-methyl group, 19-nor-3-oxo-4-ene steroids gave decreased stereoselectivity for 5β-ketones in basic medium; rather, high yields of 5β-ketone were obtained in the hydrogenation in acidic medium, similar to $\Delta^{1,9}$-2-octalone, where high yields of *cis*-2-decalone were obtained in acidic medium as described above.[252] The action of hydrobromic acid to increase the formation of 5β compounds has been found to be most effective when used in tetrahydrofuran. The amounts of hydrobromic acid required for obtaining an optimal selectivity to 5β were also much smaller in tetrahydrofuran than in a hydroxylic solvent. It is noted that the stereoselectivities obtained were even higher in tetrahydrofuran-hydrobromic acid than in the acetic acid–hydrobromic acid system.[255] Thus, 19-norandrost-4-ene-3,17-dione (eq. 3.77), 19-nortestosterone, and its acetate were hydrogenated to the corresponding saturated 5β-ketones in 97.9, 98.6, and 99.8% yields, respectively, in the hydrogenation over palladium in tetrahydrofuran–hydrobromic acid (see also eq. 3.72). The hydrogenations of the corresponding 3-oxo-4-enes with the 10β-methyl group were less stereoselective under these conditions, giving the 5β-ketones in 84, 78, and 97% yields, respectively.[267]



(3.77)

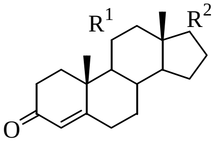
It is well known that some functional groups, such as an oxo or a hydroxyl, which are located far from the 4,5-double bond e.g., at C11, C17, or C20, may have a marked effect on the stereochemistry of hydrogenation of 3-oxo-Δ^4-steroids. In some cases 5α-ketones are formed predominantly.[268] A typical example is the hydrogenation of cortisone acetate (**116**) over 5% Pd–C in ethyl acetate (eq. 3.78).[269] No evidence was obtained for the presence of 5β derivative in the product.



(3.78)

Mori et al. estimated, quantitatively by means of GC analysis, the effects of the functional groups at C11, C17, and C20 on the 5β/5α ratios of the resulting saturated ketones in the hydrogenation of twenty-five 3-oxo-4-ene steroids over a palladium black in *i*-PrOH, *i*-PrOH-HCl, AcOH, and AcOH–HCl at 25°C and atmospheric pressure.[270] Isopropyl alcohol was used as the solvent, instead of ethanol, to avoid acetal formation.[189] The results are summarized in Table 3.18. The effect of a substituent to increase the proportion of 5β isomer was defined as positive and the reverse effect as negative, on the basis of the results with the corresponding parent steroids without the substituent. The 5β/5α ratio obtained in the hydrogenation of cholest-4-ene with a

TABLE 3.18 The Ratio of 5β K Kβ to 5α Ketone from Hydrogenation of 3-Oxo-4-ene Steroids over Palladium Catalyst[a,b]



	Solvent			
	i-PrOH	*i*-PrOH/HCl	AcOH	AcOH/HCl
$R^1 = R^2 = H$	1.0	0.95	1.1	3.4
$R^1 = H$; R^2 = α-OH	4.1	4.0	3.2	2.3
$R^1 = H$; R^2 = α-OAc	2.7	2.9	2.7	3.1
$R^1 = H$; R^2 = α-OBz	3.5	3.5	6.9	8.8
$R^1 = H$; R^2 = β-OH	0.73	0.57	0.84	0.63
$R^1 = H$; R^2 = β-OAc	1.9	2.3	1.3	2.5
$R^1 = H$; R^2 = β-OBz	1.5	1.3	2.6	3.1
$R^1 = H$; R^2 = =O	0.55	0.91	1.3	1.3
R^1 = β-OH; R^2 = β-OAc	0.62	0.48	1.3	2.0
R^1 = =O; R^2 = β-OAc	0.13	0.20	0.30	0.47
R^1 = β-OH; R^2 = =O	0.26	0.19	0.69	1.0
R^1 = β-OAc; R^2 = =O	0.27	0.33	0.91	1.1
R^1 = =O; R^2 = =O	0.09	0.07	0.17	0.27
$R^1 = H$; R^2 = β-C_8H_{17}	1.5	0.86	0.89	3.9
$R^1 = H$; R^2 = β-C_2H_5	2.7	1.2	2.2	3.5
$R^1 = H$; R^2 = β-CH(α-OH)CH_3	1.3	0.67	2.3	1.6
$R^1 = H$; R^2 = β-CH(α-OAc)CH_3	0.58	0.37	2.8	2.3
$R^1 = H$; R^2 = β-CH(β-OH)CH_3	1.4	1.0	1.7	2.5
$R^1 = H$; R^2 = β-CH(β-OAc)CH_3	1.0	0.67	0.98	2.7
$R^1 = H$; R^2 = β-$COCH_3$	0.34	0.21	0.48	0.62
R^1 = α-OH; R^2 = β-$COCH_3$	0.38	0.28	0.59	0.66
R^1 = α-OAc; R^2 = β-$COCH_3$	0.71	0.28	0.68	1.1
R^1 = β-OH; R^2 = β-$COCH_3$	0.16	0.08	0.32	0.35
R^1 = β-OAc; R^2 = β-$COCH_3$	0.33	0.22	0.84	0.86
R^1 = =O; R^2 = β-$COCH_3$	0.03	0.02	0.04	0.04

[a]Data of Mori, K.; Abe, K.; Washida, M.; Nishimura, S.; Shiota, M. *J. Org. Chem.* **1971**, *36*, 231. Reprinted with permission from American Chemical Society.

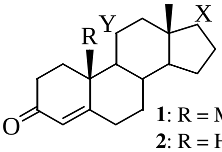
[b]The compound (10 mg) was hydrogenated in the solvent (10 ml) with prereduced palladium hydroxide (5 mg) at 25°C and atmospheric pressure. For the hydrogenations in the presence of acid, 0.05 ml of 3*M* hydrochloric acid was added after the catalyst had been prereduced in *i*-PrOH or AcOH.

17β-C_8H_{17} side chain was almost the same with that from androst-4-ene-3-one with no substituent at C17, while the 17β-ethyl group had a slight positive effect. With respect to the hydroxyl substituents, 11α, 20α, and 20β groups had almost no effect or slightly negative effects, while the 17α-hydroxyl group had a positive effect. On the other hand, both 11β- and 17β-hydroxyl groups showed significantly negative effects. Thus, the effects of the hydroxyl groups to increase the formation of 5β derivatives may be ordered as follows: 17α-OH > 11α-OH > H > 20α-OH ≅ 20β-OH > 17β-OH ≅ 11β-OH. Among the oxo groups, the 17-oxo had a small negative effect, while the 11- and 20-oxo groups had definitely greater negative effects that were also much greater than those of the corresponding β-hydroxyl groups. The effects of the oxo groups may be ordered as follows: H > 17-oxo > 20-oxo > 11-oxo. The least 5β/5α ratios of the product (0.02–0.04 or 98–96% 5α compound) were obtained in the case of 11-oxoprogesterone with 11- and 20-oxo groups. Concerning the acetoxyl function, the 11β- and 17β-acetoxyl groups had definitely less negative effects than the corresponding β-hydroxyl groups, while 17α-acetoxyl group showed a strongly positive effect in AcOH–HCl. The order in the effects of the acetoxyl groups was as follows: 17α-OAc > 17β-OAc ≅ 11α-OAc > H > 11β-OAc > 20α-OAc ≅ 20β-OAc. By considering the conformation of the hydroxyl groups and the magnitude of their effects, the substituent effects of the hydroxyl groups have been suggested to be electronic rather than steric, similar to those suggested by Kirk and Hartshorn for a large negative effect of the oxo group.[271]

Sidová et al. studied the long-range effects of 17-substituents on the stereochemistry of hydrogenation of Δ^4-3-oxo steroids in a series of testosterone and epitestosterone esters with carboxylic acids of varying alkyl chain length (C_1–C_{18}) over platinum oxide in acetic acid at room temperature and atmospheric hydrogen pressure.[272] In 17α-esters the 5α/5β ratio decreased with increasing length of alkyl chain from 0.29 with a C_1 ester to 0.12 with a C_{18} ester, whereas in 17β-esters the ratio did not vary much up to decanoate (mostly within 0.4–0.5) and then rose sharply to 0.69 with C_{12} ester and to 1.0 with a C_{18} ester except a low value of 0.42 with C_{14} ester. It has been noted that the difference in the 5α/5β ratio between the corresponding 17α- and 17β-series esters suggests that hydrophobic interactions may play a role in the hydrogenation of the esters.

Nishimura et al. studied the rates of hydrogenation of various 3-oxo-4-ene steroids with and without 10β-methyl group over palladium in pyridine and in tetrahydrofuran (THF)–hydrobromic acid, in order to ascertain the effects of the 10β-methyl group and some oxygen functions (=O, OH, OAc) at positions C11, C17, and C20.[267] As seen from the results summarized in Table 3.19, the rates of hydrogenation are greatly depressed by the presence of 10β-methyl group in THF–hydrobromic acid, while the effects on the rate are only slight in pyridine (compare compounds **1c**, **1d**, and **1e** with **2c**, **2d**, and **2e**). The facts that in pyridine the effects of the 10β-methyl group on the rates are rather small and the stereoselectivities decrease with 19-nor steroids have suggested that the transition state that might control the product would be in an sp^3-like conformation at the C5, where the interaction of the 10β-methyl group and the catalyst surface would not be great in the transition state leading to the 5β products,

TABLE 3.19 Rates of Hydrogenation and Selectivities for 5β-Ketone in Hydrogenation of 3-Oxo-4-ene and 19-Nor-3-oxo-4-ene Steroids over Palladium Catalyst in Pyridine and in Tetrahydrofuran/Hydrobromic Acid[a,b]



1: R = Me
2: R = H

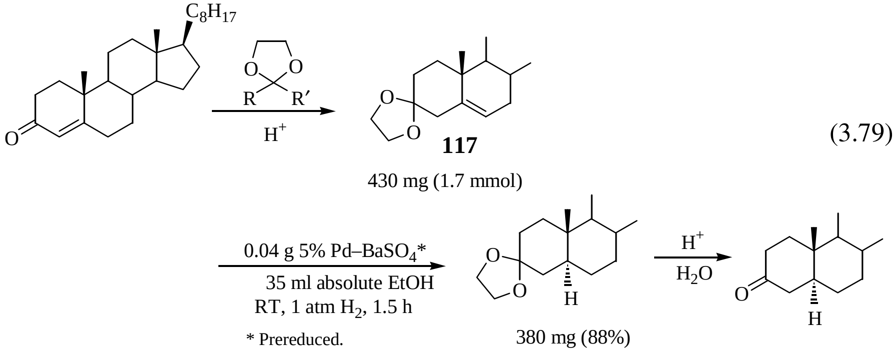
			Hydrogenation in Pyridine			Hydrogenation in THF/HBr		
Compound	X	Y	10^4k (mol·min^{-1}· g cat^{-1})[c]	k/k_{1a}	Selectivity for 5β (%)	10^4k (mol·min^{-1}· g cat^{-1})	k/k_{1a}	Selectivity for 5β (%)
1a	β-C_8H_{17}	H	1.0	1.0	99	0.98	1.0	98.5
1b	H	H	1.2	1.2	95	0.98	1.0	94
1c	β-OAc	H	1.8	1.8	98.5	0.98	1.0	97
1d	β-OH	H	2.1	2.1	93	1.5	1.5	78
1e	=O	H	2.4	2.4	92.5	1.4	1.4	84
1f	β-$COCH_3$	H	2.6	2.6	86	1.8	1.8	79
1g	=O	=O	4.1	4.1	32	2.6	2.7	30
2c	β-OAc	H	1.8	(1.0)[d]	95	13	(13)[d]	99.9
2d	β-OH	H	2.4	(1.1)[d]	85	12	(8.1)[d]	98
2e	=O	H	2.8	(1.2)[d]	89	13	(9.3)[d]	98

[a]Data of Nishimura, S.; Momma, Y.; Kawamura, H.; Shiota, M. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 780. Reprinted with permission from Chemical Society of Japan.
[b]The compound was hydrogenated in 0.0316*M* solution (1.8 ml) with 3 mg of Pd black at 25°C and atmospheric pressure. THF (1.8 ml) contained 0.2 ml of 48% hydrobromic acid.
[c]Per gram of catalyst.
[d]The figures in parentheses indicate the ratio of the rate for 19-nor steroid to that for the corresponding 10β-methyl analog.

while the transition state leading to 5α products would be more stable in 19-nor steroids than in 10β-methyl steroids because of lack of an interaction between axial 2β-hydrogen and 10β-methyl in 19-nor steroids. On the other hand, the rate as well as the selectivity to 5β product increased greatly with 19-nor steroids in THF–hydrobromic acid, compared to the corresponding 10β-methyl steroids. These results have suggested that the product-controlling transition state in THF–hydrobromic acid is in an sp^2-like conformation where the attack of hydrogen from the β face would be not as hindered with 19-nor steroids as with the usual steroids of the 10β-methyl group. The rate measurements and competitive hydrogenations also indicated that the compounds having the oxygen functions, which decreased the 5β/5α ratios of the product, were generally more reactive than those not carrying such functions in both pyridine and in THF–hydrobromic acid. In particular, the compound **1g** with 11,17-dioxo group is noteworthy in that, in both basic and acidic media, it was definitely more reactive and gave much lower yields of 5β product than did the other compounds investigated. Since high stereoselectivities to 5β are generally obtained in both basic and acidic media in which a polarized adsorption of the 3-oxo-4-ene system may become favorable,

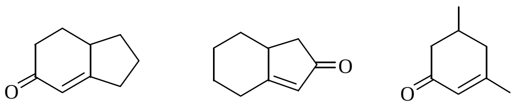
it has been suggested that the electron-attractive oxygen functions may work in opposition to the π-electron polarization of the 3-oxo-4-ene group, as suggested by Kirk and Hartshorn for a 4β,5β-bonded surface complex.[273] The hydrogenation in a less polarized state would result in an increased rate as well as in a decreased 5β/5α ratio of the product. This explanation has been further supported by the fact that the 5β/5α ratio of the product obtained in the hydrogenation of **1g** in THF was increased neither in pyridine nor in the presence of hydrobromic acid, in contrast to the cases with the other compounds.

Compared to the hydrogenation to 5β-ketones, the hydrogenation of 3-oxo-Δ^4 steroids to 5α-ketones is much more difficult over usual heterogeneous catalysts, except in the special cases where the presence of oxo groups may favor the formation of 5α compounds as described above. Dauben, Jr. et al. obtained 5α-cholestan-3-one from cholest-4-en-3-one via transformation into 3-ethylenedioxy Δ^5-derivative **117** by exchange dioxolanation, followed by hydrogenation with palladium catalyst to give exclusively 3-ethylenedioxy-5α-cholestane (eq. 3.79).[274] The ethylenedioxy compound may be hydrolyzed quantitatively to the 5α-ketone in the presence of acid.



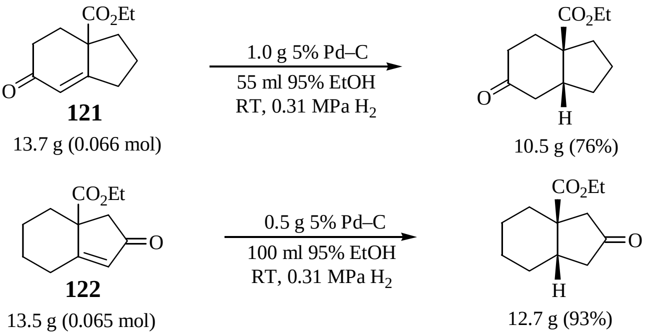
(3.79)

Hydrogenation of tetrahydroindanones **118** and **119** as well as 3,5-dimethylcyclohex-2-enone (**120**) over 5% Pd–C gives the saturated *cis*-ketones quantitatively under neu-



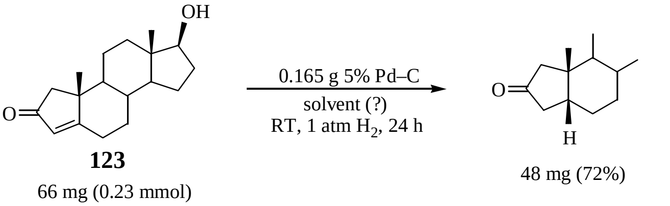
118 **119** **120**

tral (EtOH), acidic (EtOH/HCl), and alkaline (EtOH/KOH) conditions.[275] The tetrahydroindanones **121** and **122** with an ethoxycarbonyl group at the ring juncture also gave the *cis* compounds in high yields in acidic, basic, or neutral solution (eq. 3.80),[276] in contrast to the corresponding $\Delta^{1,9}$-2-octalone analog, where the *trans* product was formed in high yield (see eq. 3.73).[260,261]

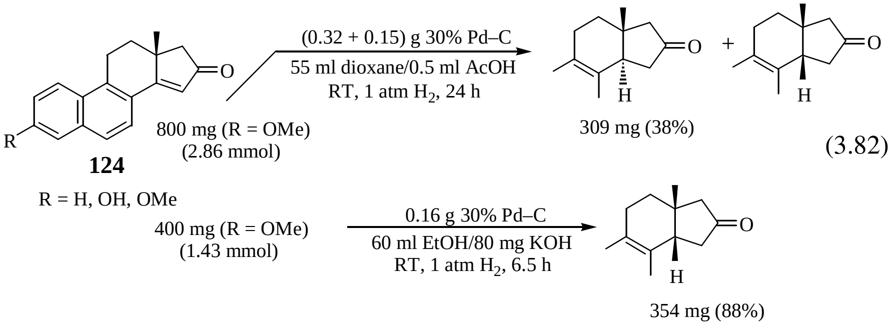


(3.80)

Similarly, hydrogenation of A-nortestosterone (**123**) gave only the A/B *cis*-fused product in high yield (eq. 3.81).[277] It is also of interest that the lithium–ammonia reduction of **123** afforded approximately equal amounts of A/B *cis*- and A/B *trans*-fused products, whereas in the reduction of testosterone with the same reagents only the A/B *trans*-fused product was isolated. On the other hand, hydrogenation of 14,15-unsaturated 16-equilenones (**124**) over Pd–C in neutral solvent led to a mixture of C/D *cis*- and C/D *trans*-fused products with the *trans* isomer apparently predominating. The proportion of *trans* isomer further increased in dioxane containing a trace of acetic acid and the isomer could be isolated in a 38% yield in the case of **124**, R = OMe. In contrast, the hydrogenation of **124** in the presence of potassium hydroxide gave the *cis* products in excellent yields (eq. 3.82).[278]



(3.81)

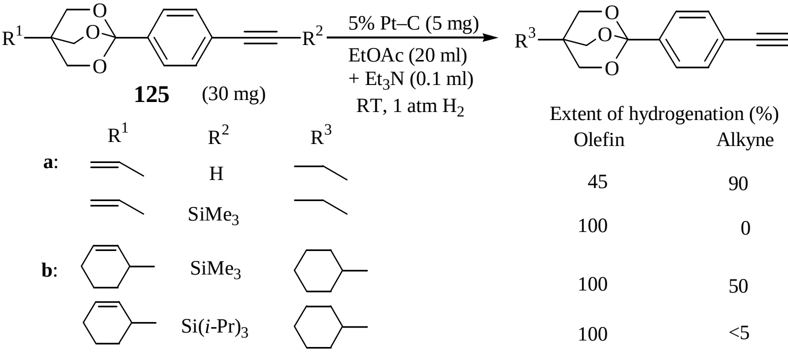


(3.82)

3.8.4 An Olefin Moiety in the Presence of Terminal Alkyne Function

Terminal triple bonds are usually hydrogenated in preference to terminal or internal double bonds in competitive conditions, unless the former bonds are highly hindered,

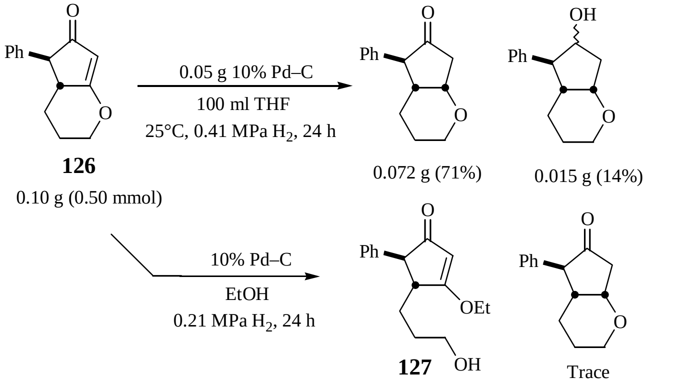
because of a strong adsorption of the triple bonds over the double bonds.[279] However, Palmer and Casida were successful for selectively hydrogenating such an olefin moiety by blocking terminal alkynes with a trimethyl- or triisopropylsilyl group, a bulky and easily removable moiety.[280] The compound **125a** with an allyl group was thus selectively hydrogenated at the olefinic moiety, using 5% Pt–C in dry ethyl acetate containing triethylamine to prevent acid-catalyzed trioxabicyclooctane ring opening (eq. 3.83). After the hydrogenation of the olefinic group was complete, some hydrogenation of the alkyne group resulted with longer reaction times. Selective hydrogenation of the compound **125b** with a cyclohexenyl moiety was more difficult to achieve, but the desired selectivity was obtained using a more bulky silyl group such as triisopropylsilyl. Desilylation was accomplished quantitatively with use of tetrabutylammonium fluoride.



(3.83)

3.8.5 β-Alkoxy-α,β-Unsaturated Ketones (Vinylogous Esters)

The hydrogenation of enol ethers, enol esters, and enol lactones may be accompanied by the hydrogenolysis of the carbon–oxygen bond. The extent of hydrogenolysis greatly depends on the structure of substrate, catalyst, and solvent, as discussed in Section 13.1.5. Usually the hydrogenolysis occurs most extensively over platinum, and palladium catalysts are preferred for avoiding or minimizing such hydrogenolysis.



(3.84)

The alkoxy group in β-alkoxy-α,β-unsaturated ketones is liable to hydrogenolysis in the hydrogenation to give β-alkoxy ketones, which are also very labile to hydrogenolysis or loss of alcohol to give α,β-unsaturated ketones, especially under acidic conditions or over catalysts containing no alkaline substances. Hydrogenation of the compound **126**, however, was successful when THF was used as the solvent instead of ethanol (eq. 3.84).[281] Hydrogenation in ethanol led to only vinylogous transesterification product **127**.

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CHAPTER 4

Hydrogenation of Alkynes

Hydrogenation of the carbon–carbon triple bonds, particularly to the olefinic bonds, has been the subject of numerous investigations since the very early stage of the study on catalytic hydrogenation, not only in terms of its synthetic utility but also with respect to the selectivity of catalytic metals for the semihydrogenation.[1–6]

In general, acetylenes are readily hydrogenated to give saturated compounds over a variety of catalysts under mild conditions with uptake of 2 mol of hydrogen. Uptake of the second mole of hydrogen is often more rapid than that of the first. However, the intermediate olefins are usually formed very selectively as long as the starting acetylenes remain, because the acetylenes are adsorbed to the catalyst much more strongly than the corresponding olefins and may effectively displace the olefins formed on the catalyst surface to prevent their further hydrogenation to saturated compounds. However, in order to obtain high yields of olefins, the second stage of the hydrogenation must remain blocked even after the starting acetylenes have been consumed completely. In practice, it is important to select a proper catalyst in combination with an appropriate modifier as well as suitable reaction conditions for obtaining a high selectivity and yield of olefins. The hydrogenation of acetylenes is a highly exothermic reaction, as seen from the heats of hydrogenation shown in Scheme 4.1.[7] Therefore, the hydrogenations must be controlled carefully for the rise in reaction temperature, especially in large-scale runs and/or in use of large amounts of catalyst. As an example, control of temperature within the range of 20–40°C was critical for clean and self-terminating semihydrogenation of *tert*-ethynyl alcohols, RR′C(OH)C≡CH, over 5% Pd–$BaCO_3$ in petroleum ether at 0.34 MPa initial hydrogen pressure. Overhydrogenations occurred when the temperature rose above 40°C.[8]

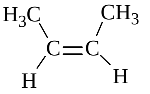
Bond and Wells studied the selectivity of group VIII metals in the vapor-phase hydrogenation of acetylene, methylacetylene, and dimethylacetylene over alumina-supported catalysts.[4,5] The selectivity in acetylene hydrogenation decreased with respect to catalyst metal in the following order: Pd >> Rh ≥ Pt > Ru >> Ir > Os. It was also noted that the high selectivity of Pd was independent of conversion while in the case of Ir it decreased considerably with increasing conversion. The initial selectivities observed in the hydrogenation of dimethylacetylene were generally much higher than in the case of acetylene. The selectivity of 1.0, as expressed by the ratio of alkene/(alkene + alkane), was obtained with Fe, Co, Ni, and Pd. The value decreased to 0.99 for Rh, 0.97 for Pt and Ru, 0.96 for Ir, and 0.90 for Os. Bond and Wells interpreted the selectivity pattern of the transition metals for acetylene hydrogenation in terms of two factors: (1) the activity for ethylene hydrogenation (kinetic factor) and (2) the thermodynamic factor, which is related to the relative strength of adsorption

$$HC{\equiv}CH + H_2 \longrightarrow H_2C{=}CH_2 + 42.3\ \text{kcal}\ (177\ \text{kJ})$$

$$HC{\equiv}CH + 2\,H_2 \longrightarrow H_3C{-}CH_3 + 74.9\ \text{kcal}\ (313\ \text{kJ})$$

$$H_3CC{\equiv}CH + H_2 \longrightarrow H_3CCH{=}CH_2 + 39.6\ \text{kcal}\ (166\ \text{kJ})$$

$$H_3CC{\equiv}CH + 2\,H_2 \longrightarrow CH_3CH_2CH_3 + 69.5\ \text{kcal}\ (291\ \text{kJ})$$

$$H_3CC{\equiv}CCH_3 + H_2 \longrightarrow$$  $$+ 37\ \text{kcal}\ (155\ \text{kJ})$$

$$H_3CC{\equiv}CCH_3 + 2\,H_2 \longrightarrow CH_3CH_2CH_2CH_3 + 65.6\ \text{kcal}\ (274\ \text{kJ})$$

Scheme 4.1 Heats of hydrogenation of acetylene, methylacetylene, and dimethylacetylene (82°C).

of acetylene and ethylene. The high selectivities of iron, cobalt, and nickel were attributed to their lowest activities for ethylene hydrogenation, as reported by Beeck[9] and Schuit and van Reijen.[10] The high selectivity of palladium, which was higher than that of nickel, was explained by assuming a powerful thermodynamic factor that would be operative over palladium, because its activity for ethylene hydrogenation is higher than nickel.[5] It is also noted that palladium with the highest selectivity for acetylene hydrogenation also shows the highest activity for olefin hydroisomerization.[11,12] Similarly, the lowest selectivities of osmium and iridium are in line with their lowest activities for olefin isomerization.[11,12] Thus, to what extent the thermodynamic factor is operative on a metal in acetylene hydrogenation appears to be most closely related to the characteristic behavior of the metal for olefin isomerization.

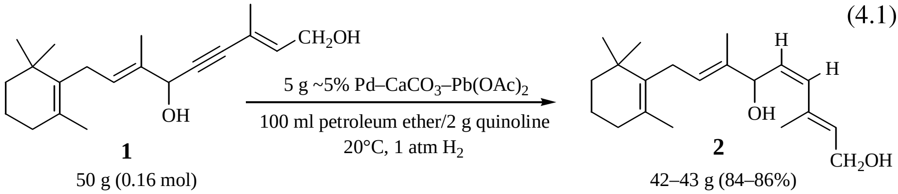
4.1 HYDROGENATION OVER PALLADIUM CATALYSTS

Palladium catalysts, usually in combination with support and/or inhibitor, have been most widely utilized among the transition metals for the selective hydrogenation of acetylenes. Colloidal palladium, which had been recognized as more selective than platinum and palladium black, was extensively used in early investigations, in particular by Paal, Zalkind, and Bourguel in the liquid-phase hydrogenation of various acetylenic compounds at room temperature.[13] Over colloidal palladium, the products resulting from *cis* addition of hydrogen were obtained by hydrogenation of disubstituted acetylenes such as phenylpropiolic acid, tolan (diphenylacetylene), and tetraalkylbutynediol.[14–17] In later studies, however, use of colloidal palladium has been almost completely displaced by supported palladium catalysts, such as those supported on calcium carbonate, barium carbonate, barium sulfate, or carbon, usually in combination with an appropriate catalyst poison, because of the convenience in their preparation and use in hydrogenation.

Supported palladium catalysts have often been used with an organic base such as pyridine and quinoline as additive or solvent to depress hydrogenation of resulting olefins and thus improve selectivity. For example, the selective hydrogenation of steroidal 17-

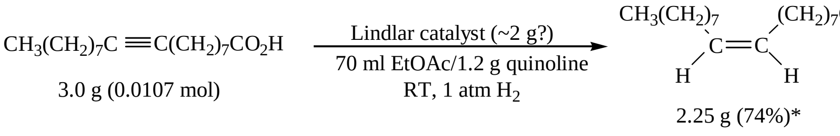
ethynyl group to the vinyl group was effectuated by using a Pd–$CaCO_3$ in pyridine solution.[18,19] Isler et al. used a Pd–C poisoned by quinoline in methanol for the partial hydrogenation of an acetylenic intermediate **1** with a conjugated enyne system to **2** with a conjugated diene, as a key step leading to the synthesis of vitamin A.[20] One of the most selective catalyst systems is probably the one by Lindlar, who poisoned a Pd–$CaCO_3$ catalyst with $Pb(OAc)_2$ solution and used it in petroleum ether with addition of quinoline, and thus improved the selectivity of the partial hydrogenation of **1** (eq. 4.1).[21]

(4.1)



Originally, Lindlar activated a $Pd(OH)_2$–$CaCO_3$ catalyst with hydrogen, but later the procedure has been improved by using sodium formate as a reducing agent.[22] It appears that the improved procedure gives a catalyst with a more uniformly dispersed metal on the support, as judged from the color of the resulting catalyst.[23] Dobson et al. studied the stereoselectivity of the hydrogenation of 4-undecyne over various palladium catalysts.[24] Almost pure *cis*-4-undecene was produced only when Lindlar catalyst was used. In all other cases, rather high percentages of the *trans* isomer were formed, although the hydrogenations were stopped when 1 equiv of hydrogen had been absorbed (Table 4.1). Similarly, 2-heptene and 5-decene containing only 1 and 5% of the *trans* isomers, respectively, were obtained by hydrogenation of 2-heptyne and 5-decyne in the presence of Lindlar catalyst.

Baker et al. studied the stereoselective semihydrogenation of acetylenic fatty acids using the Lindlar catalyst.[25] Thus, when stearolic acid was hydrogenated over Lindlar catalyst in ethyl acetate, 1 mol of hydrogen was absorbed rapidly and then the reaction became extremely slow. There was no indication of the presence of any significant quantities ($< 2.5\%$) of stearic or stearolic acid in the crude product. The oleic acid obtained in 74% yield by crystallization of the product was found to contain about 5% of *trans*-olefinic bond as examined by IR spectroscopy (eq. 4.2), but no migration of the unsaturated bond had occurred, as was shown by means of ozonolysis. The formation of *trans* product was reduced to ~1–2% by doubling the amount of added quinoline. Similarly, erucic acid (*cis*-13-docosenoic acid) was obtained in 88% yield by hydrogenation of behenolic acid over Lindlar catalyst in ethyl acetate.



(4.2)

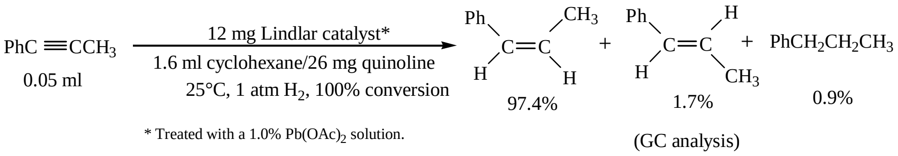
* Containing ~5% *trans*.

TABLE 4.1 Percent *Trans* Isomer in Olefinic Product with Uptake of 1 mol of Hydrogen by 4-Undecyne in the Presence of Palladium Catalysts[a,b]

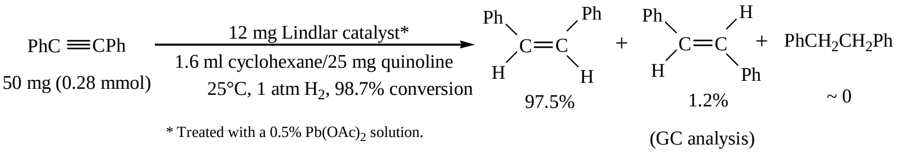
	Catalyst							
	4.8% Pd–$CaCO_3$–$Pb(OAc)_2$[c]	10% Pd–$CaCO_3$	10% Pd–$BaSO_4$	10% Pd–C	10% Pd–C[d]	10% Pd–C[d]	10% Pd–C + Et_3N[e]	10% Pd–C + AcOH[f]
% Catalyst	8.9	10.1	11.2	9.8	10	17.4	11.5	10.5
%*Trans* in olefinic content	4	63	40	32	68	31	17	49

[a]Data of Dobson, N. A.; Eglinton, G.; Krishnamurti, M.; Raphael, R. A.; Willis, R. G. *Tetrahedron* **1961**, *26*, 16. Reprinted with permission from Elsevier Science.
[b]The substrate (about 0.02 mol) was hydrogenated at room temperature and 1 atm H_2 in ethyl acetate, unless otherwise stated. In all cases hydrogen uptake slowed when 1 equiv of hydrogen had been absorbed (the experiment was then stopped) but ceased spontaneously only with the Lindlar catalyst.
[c]Lindlar catalyst; a few drops of quinoline were added to the hydrogenation mixture.
[d]Cyclohexane as solvent and Baker catalyst (all other cases, Johnson Matthey) were used.
[e,f]0.5 ml of Et_3N and AcOH were added, respectively.

It is to be noted that the Lindlar catalyst should be used in an aprotic solvent because the effects of the poisons may be decreased in protic solvents. Unsatisfactory results obtained with use of the Lindlar catalyst appear to be those cases where hydrogenations were performed using alcoholic solvents.[26–28] The concentration and/or amount of lead acetate solution should also be adjusted, depending on the nature of substrates, to avoid poisoning the Pd–$CaCO_3$ catalyst too strongly. It was often observed that hydrogenations over Lindlar catalyst proceeded not at all or only very slowly.[29] In the hydrogenation of 1-phenyl-1-propyne and diphenylacetylene in cyclohexane, treatment of the Pd–$CaCO_3$ with 1.0 and 0.5% of $Pb(OAc)_2$ solution (instead of 1.8% described in the literature [22]), respectively, was sufficient to inhibit the hydrogenation of the resulting alkenes and to obtain high yields of the corresponding *cis*-alkenes (eqs. 4.3[23] and 4.4[30]).

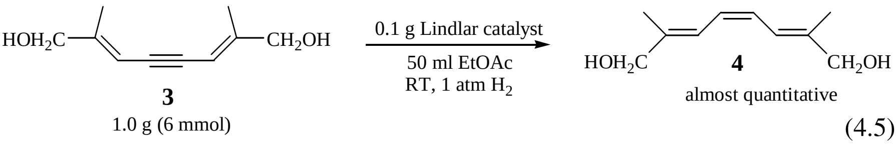


(4.3)



(4.4)

The effects of added quinoline alone and of added quinoline with $Pb(OAc)_2$ in the hydrogenation of diphenylacetylene in cyclohexane are shown in Figs. 4.1*a–c*. It is seen that over Lindlar catalyst in the presence of quinoline, the formation of diphenylethane as well as the isomerization of *cis*-stilbene to the *trans* isomer were inhibited almost completely as long as 4 h after the hydrogenation of diphenylacetylene to stilbene had been practically completed within 1 h. The Lindlar catalyst was found to be as highly selective as a homogeneous catalyst, $[Rh(NBD)(PPhMe_2)_3]^+ PF_6^-$, which is known highly selective in alkyne hydrogenation,[31] when compared in the hydrogenation of diphenylacetylene (in acetone with the rhodium complex).[32] Another example that shows high selectivity of Lindlar catalyst when employed in aprotic solvent is seen in eq. 4.5 in the hydrogenation of the glycol **3** with a conjugated dienyne system to a triene glycol **4**.[33] The triene glycol **4** was obtained almost quantitatively in the hydrogenation in ethyl acetate, while another group obtained only a 47.5% yield of **4** in the same hydrogenation using methanol as solvent.[26]



(4.5)

A new Pd–Pb alloy catalyst has been reported to be more selective than commercial Lindlar catalyst in the hydrogenation of triple bonds, that is, in the hydrogenation of 2-butyne to (*Z*)-2-butene and phenylacetylene to styrene.[34] The high selectivity of the alloy catalyst was confirmed in the syntheses of (*Z*)-11-hexadecenyl acetate and (*Z*)-11-tetradecenyl acetate where particularly high stereoselectivity was required.

Compared to disubstituted acetylenes, the selective hydrogenation becomes more difficult in monosubstituted acetylenes, especially in the cases where the product has a highly reactive terminal double bond. Thus, Lindlar and Dubuis noted that the hydrogenation of phenylacetylene did not stop at the uptake of 1 equiv of hydrogen even over the Lindlar catalyst of the standard preparation, although hydrogen absorption abruptly slowed after that stage.[22] The hydrogenation of 1-phenyl-1-propyne and diphenylacetylene over Lindlar catalyst practically did not proceed further after uptake of 1 equiv of hydrogen, as seen in eqs. 4.3 and 4.4 and Fig. 4.1*c*.

Semihydrogenations of conjugated enynes are seldom selective and tend to give mixtures even over Lindlar catalyst.[6,35] Marvell and Tashiro studied the selectivity in semihydrogenation of three conjugated enynes **5**, R = H, Me, Et (eq. 4.6), and one conjugated dienyne **6** (eq. 4.7) over Lindlar catalyst in petroleum ether.[36] In no case did the rate of hydrogen uptake show a break after absorption of 1 equiv of hydrogen; therefore, the products were analyzed by interrupting the hydrogenations after uptake of 1 mol of hydrogen. Probably semihydrogenation of the dienyne **6** would be one of the most difficult cases because **6** contains an internal triple bond conjugated with a terminal double bond, as indicated by the results that the yield of the triene **7** was only 54%. Rather low stereoselectivities for the *cis* isomers may also be related to the com-

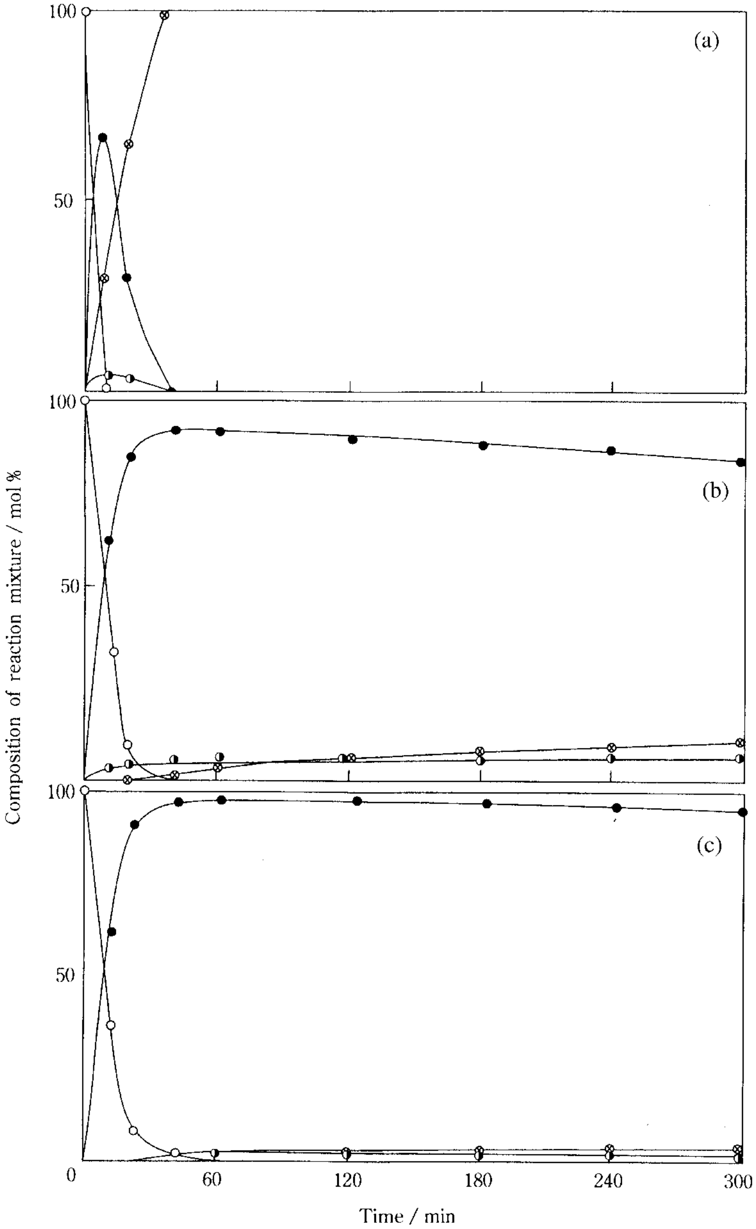
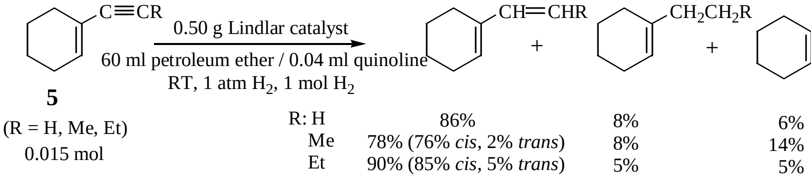
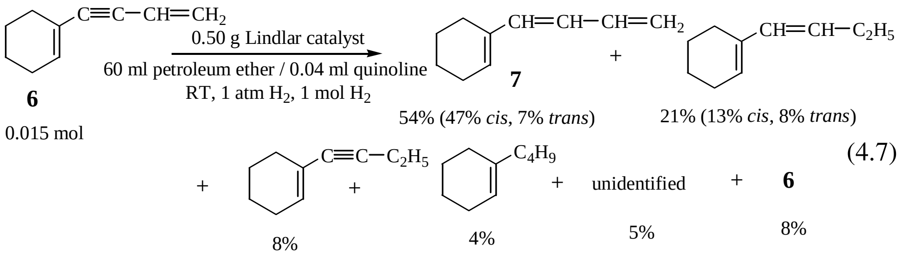


Figure 4.1 The effects of $Pb(OAc)_2$ and quinoline on the hydrogenation of diphenylacecylene over $Pd–CaCO_3$ (Lindlar). Diphenylacetylene (50 mg) was hydrogenated over $Pd–CaCO_3$ (12 mg) in cyclohexane (1.6 ml) at 25°C and 1 atm H_2. (a) $Pd–CaCO_3$; (b) $Pd–CaCO_3$+quinoline (25 mg); (c) $Pd–CaCO_3/Pb(OAc)_2$/quinoline. (Key: ○ diphenylacetylene; ● *cis*-stilbene; ◑ *trans*-stilbene; ⊗diphenylethane.) (From Nishimura, S.; Takagi, Y. *Catalytic Hydrogenation. Application to Organic Synthesis*; Tokyo Kagaku Dozin:Tokyo, 1987; p 151. Reproduced with permission of Tokyo Kagaku Dozin Co., Ltd.)

petitive hydrogenation of the reactive double bond even in the presence of the unreduced triple bond.



(4.6)



(4.7)

In some other hydrogenations, satisfactory results were obtained with palladium catalysts other than the Lindlar. Brunet and Caubere described a highly selective palladium catalyst in the semihydrogenation of acetylenes.[28] The palladium catalyst (denoted as Pdc) was prepared from NaH, *t*-PeOH, and $Pd(OAc)_2$ in THF. The reaction mixture containing 0.2 mmol Pd per 1 ml was used for hydrogenation, withdrawn by a syringe. Table 4.2 shows examples of highly selective self-terminating hydrogenations of mono- and disubstituted acetylenes over Pdc in the presence of quinoline. In contrast to the cases with monosubstituted acetylenes, hydrogenations of disubsti-

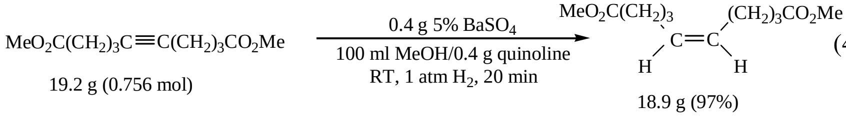
TABLE 4.2 Semihydrogenation of Acetylenes over Pdc–Quinoline[a,b]

Compound	Solvent (ml)	Olefin (%)[c]	Saturated Compound (%)[c]
Phenylacetylene	Hexane (8)	98.5	1.5
1-Octyne	Hexane (8)	98.7	1.3
1-Phenyl-1-propyne	EtOH (1)+hexane (7)	98.4 (*cis*) + 0.6 (*trans*)	1
2-Hexyne	EtOH (4)+octane (4)	97.8 (*cis*)[d] + 1.2 (*trans*)[d]	1
Diphenylacetylene	EtOH (3)+THF (5)	97.3 (*cis*) + 1.7 (*trans*)	1

[a]Data of Brunet, J.-J.; Caubere, P. *J. Org. Chem.* **1984**, *49*, 4058. Reprinted with permission from American Chemical Society.
[b]The acetylene (10 mmol) was hydrogenated over Pdc (0.2 mmol) with 2 ml of quinoline for 8 ml of solvent at an initial temperature of 20–21°C (the temperature rose to 31–33°C in the case of phenylacetylene) under atmospheric pressure.
[c]Determined by GC.
[d]Small amounts (0.1–0.2%) of 1-hexene were detected.

tuted acetylenes were performed in ethanol, ethanol–hydrocarbon, or ethanol-THF mixtures, since the hydrogenations of disubstituted acetylenes were extremely slow in hexane or octane in the presence of quinoline. The result by Litvin et al. that hydrogenation of diphenylacetylene over Lindlar catalyst gave a mixture of 93% of *cis*-stilbene, 2% of *trans*-stilbene, and 5% of diphenylethane[37] was quoted by Brunet and Caubere to indicate the superior selectivity of Pdc over Lindlar catalyst. However, it should be noted that the result by Litvin et al. was obtained using methanol as solvent, which might have led to a decreased selectivity of the Lindlar catalyst (see eqs. 4.2 and 4.3).

In the hydrogenation of dimethyl 5-decyne-1,10-dioate (eq. 4.8) and 1,7-cycododecadiyne (eq. 4.9), Cram and Allinger obtained the corresponding *cis* and *cis*,*cis* olefinic compounds, respectively, in high yields with 5% Pd–$BaSO_4$ in the presence of quinoline and noted this catalyst to be superior to the Lindlar catalyst in reproducibility and ease of preparation.[38] In the hydrogenation of tridehydro[18]annulene (**8**) to [18]annulene (**9**), Sondheimer et al. obtained better results by use of a 10% Pd–C, rather than with the Lindlar catalyst, over which the reaction often proceeded very slowly or even ceased before the required amount of hydrogen had been absorbed.[39] The optimum yield of **9** was 31–32% as analyzed by UV absorption on the uptake of 5–6 equiv of hydrogen, while 5.5% of the starting material was found unchanged when 6 equiv of hydrogen had been adsorbed in a preparative run (eq. 4.10). In a similar hydrogenation of hexadehydro[18]annulene (**10**) the best results were obtained over a Pd–$BaSO_4$ in the presence of quinoline, rather than with a 10% Pd–C or with Lindlar catalyst (eq. 4.10).[40] Since these hydrogenations involve the isomerization of *cis* to *trans* olefinic bonds, the effectiveness of Pd–C or Pd–$BaSO_4$ over Lindlar catalyst may result from their greater tendency toward the isomerization.[24]



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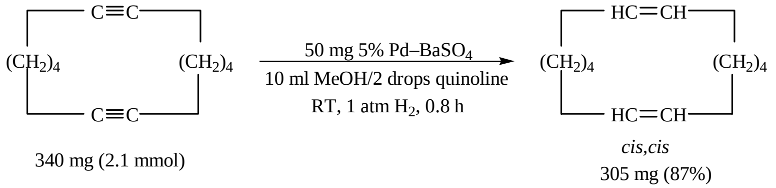
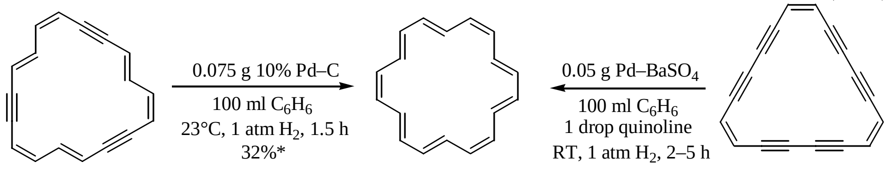


(4.9)

(4.10)


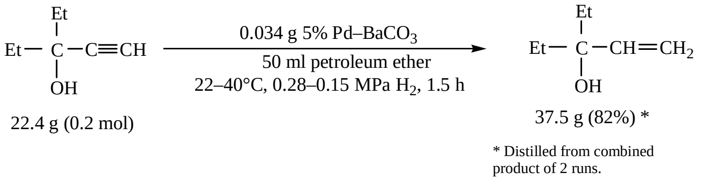
8
1.04 g (4.6 mmol)

9

10
0.25 g (1.1 mmol)

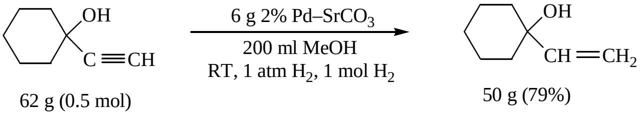
* Analyzed by UV at uptake of 6 equiv of H_2.

Because of the importance of the selective hydrogenation of alkynols and alkynediols in synthetic applications, a considerable body of studies and patents has been described in the literature on this topic. Reppe et al. used a Pd–Fe–kieselguhr catalyst mostly for vapor-phase partial hydrogenation of lower alkynols, such as propargyl alcohol and 1-butyn-3-ol. Iron (see eq 4.28) and other poisoned transition metal catalysts have been employed in the liquid-phase hydrogenation of alkynediols.[41] For the hydrogenation to saturated alkanols and alkanediols, use of Raney Ni was preferred, usually at 40–60°C and 10–20 MPa H_2. Hennion et al. accomplished the semihydrogenation of *tert*-alkynols, R,R′C(OH)C≡CH, and their acetates over a 5% Pd–$BaCO_3$ in petroleum ether under low hydrogen pressure, and obtained high yields (80–90%) of the corresponding alkenols and their acetates, merely by controlling the temperature within the range of 20–40°C with use of rather small amounts of catalyst (eq. 4.11).[8]



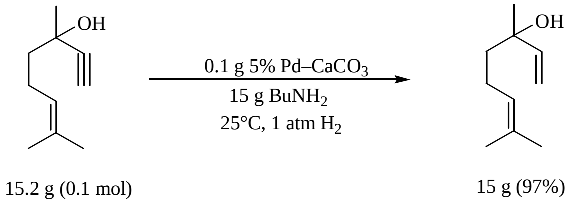
(4.11)

Robins and Walker obtained 1-vinylcyclohexanol in high yield simply by hydrogenating 1-ethynylcyclohexanol over 2% Pd–$SrCO_3$ in methanol until the calculated amount of hydrogen had been absorbed (eq. 4.12).[42]



(4.12)

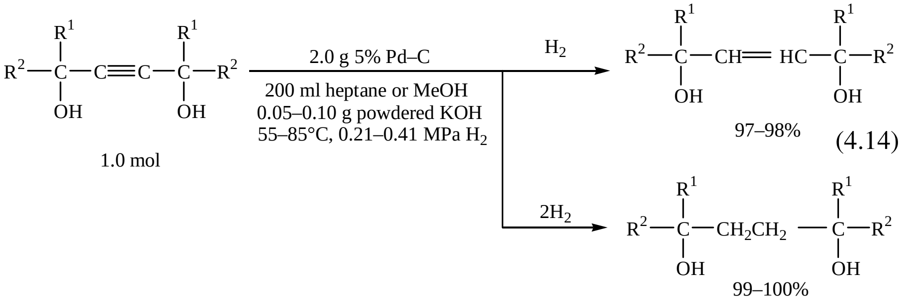
In a patent dealing with the selective hydrogenation of alkynols, use of palladium catalysts in combination with lower aliphatic amines such as butylamine, ethanolamine, and ethylenediamine, or in liquid ammonia was claimed to be more effective than use in the presence of higher amines, and superior to Lindlar catalyst in both activity and selectivity.[43] Thus, linalool was obtained almost quantitatively by hydrogenation of 3,7-dimethyl-6-octen-1-yn-3-ol over Pd–$CaCO_3$ in the presence of butylamine (eq. 4.13).



(4.13)

Fukuda and Kusama compared the effects of added pyridine, piperidine, and quinoline in the hydrogenation of 2-butyne-1,4-diol over unpoisoned and lead-poisoned Pd–$CaCO_3$ catalysts in water at room temperature and atmospheric hydrogen pressure.[44] The hydrogenation of 2-butene-1,4-diol was almost completely depressed by the addition of quinoline over both the unpoisoned and the poisoned catalysts, while the depressions by piperidine and particularly by pyridine were much less marked and limited only to the cases over the poisoned catalyst. The $CaCO_3$ as a carrier in the poisoned palladium catalysts was also shown to be effective to decrease the polymerization accompanying the hydrogenation.[45] Palladium catalysts supported on a basic or slightly acidic support and poisoned by Zn and Cu or Ag or both have been employed in a process for selective hydrogenation of 2-butyne-1,4-diol to the corresponding butenediol. A typical catalyst contained Pd 0.5, CuO 0.12, and ZnO 0.12 on δ-Al_2O_3 and gave the butenediol containing only 0.83% butanediol, 0.33% acetals, and 0.29% butynediol.[46]

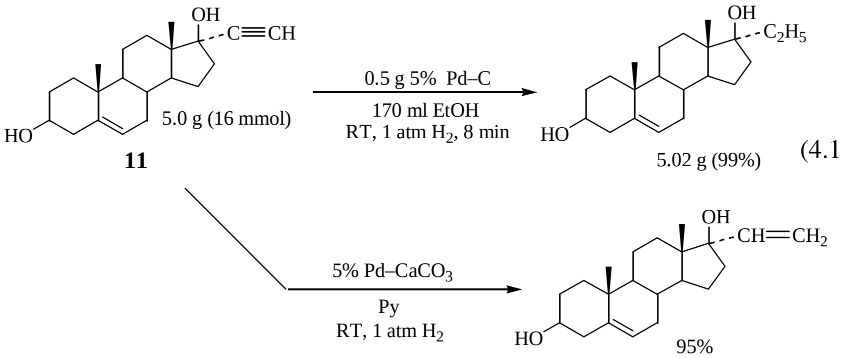
Tedeschi hydrogenated tertiary 1,4-acetylenic glycols over Pd–C in the presence of a strong base such as potassium, potassium hydroxide, or sodium hydroxide to depress the hydrogenolysis at the tertiary hydroxyl groups, which was found to occur mainly on hydrogenation of the resulting olefinic glycols rather than at the acetylenic glycols.[47] Thus, in the presence of small amounts of potassium hydroxide, high yields of olefinic or saturated glycols were obtained in the hydrogenation of acetylenic glycols by either interrupting the hydrogenation at the end of the first stage or continuing it to completion (eq. 4.14).[48] Hydrogenations in the absence of base gave the corresponding saturated diols in only 17–36% yields. Attempts to halt the hydrogenation selectively at the olefinic stage using Lindlar catalyst or small amounts of Pd–C were also unsuccessful. The conclusion that the hydrogenolysis of the activated carbon–oxygen bond did not occur on hydrogenation of the acetylenic glycols to the olefinic glycols is in accord with the results obtained in the hydrogenation of 3-phenylpropargyl alcohol over platinum oxide[49] and of 2,5-diacetoxy-2,5-dimethyl-3-hexyne over Pd–C.[50]



(4.14)

17α-Ethynyl-5-androstene-3β,17β-diol (**11**) was hydrogenated to the 17α-ethyl derivative over Raney Ni[51] or Pd–C[19] in ethanol while the 17-vinyl derivative was obtained in high yield by hydrogenation of **11** in pyridine solution using Pd–$CaCO_3$ catalyst (eq. 4.15).[19] Similarly, 3β-acetoxy-5,16-pregnadien-20-yne (**12**) and 17α-

ethynyltestosterone (**13**) were hydrogenated to the 17-ethyl derivatives (with saturation of the Δ^{16} double bond in the case of **12**) over Pd–C in ethanol or dioxane[19] and to the vinyl derivatives over Pd–$CaCO_3$ in pyridine[18,19] (eq. 4.16[19]). The use of pyridine was also advantageous since it was a good solvent for **13** which was soluble with some difficulty in the usual solvents. It is noted that the ethynyl group in **13** was selectively hydrogenated over the highly reactive 3-oxo-4-ene group with both Pd–C in dioxane and Pd–$CaCO_3$ in pyridine.



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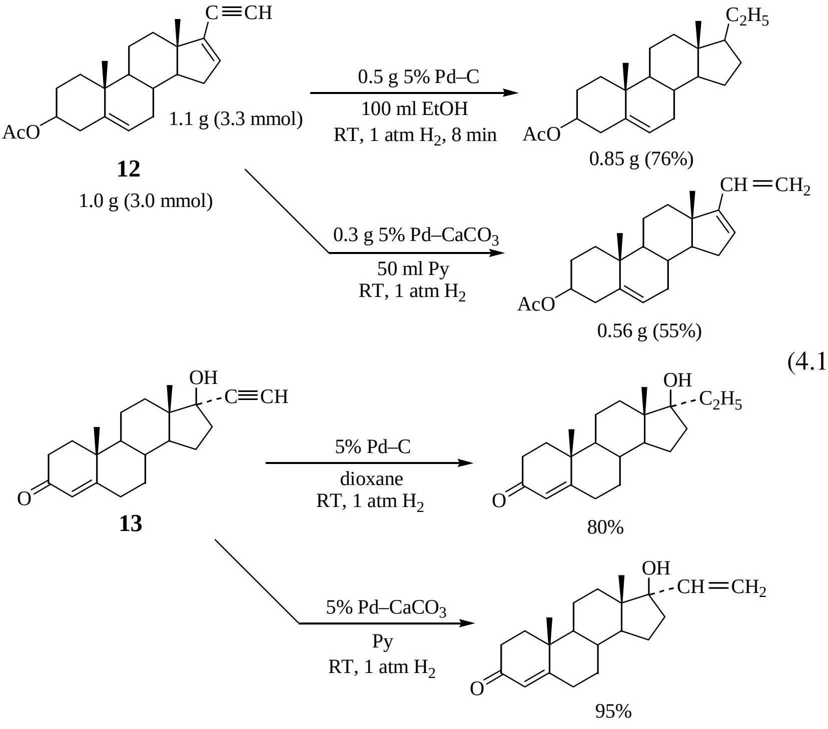
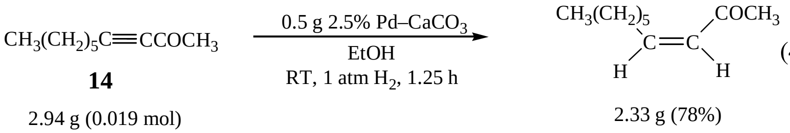


(4.16)

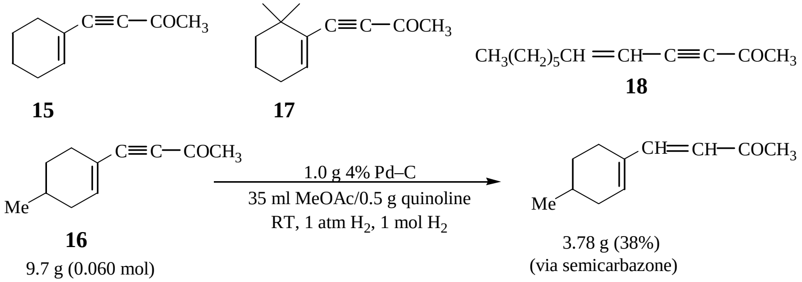
Hydrogenation of an α,β-ynone, 3-decyn-2-one (**14**), to the corresponding *cis*-enone was successful with Pd–$CaCO_3$ as catalyst (eq. 4.17).[52] It was necessary to use a rather

large amount of catalyst (~20% by weight of substrate), since slow hydrogenation tended to cause *cis*-to-*trans* isomerization. For the same reason, the less active Lindlar catalyst could not be employed in this hydrogenation. Similarly, *cis*-3-hepten-2-one and *cis*-4-cyclohexyl-3-buten-2-one were obtained in 78 and 91% yields, respectively, by hydrogenation of the corresponding ynones over Pd–$CaCO_3$ in pentane or hexane as solvent.[52,53]



(4.17)

Selective hydrogenation becomes much more difficult in cases of conjugated enynone systems. Heilbron et al. hydrogenated the enynone **15** in the presence of a quinoline-poisoned Pd–C in methanol, but the corresponding dienone could be isolated in only 20% yield as its semicarbazone, even when the hydrogenation was interrupted at the uptake of the calculated quantity of hydrogen.[54] Hydrogenation of the enynone **16** in methyl acetate under similar conditions was more successful; the corresponding dienone was obtained in 38% yield via its semicarbazone (eq. 4.18), although hydrogenation of **17** under the same conditions gave only 6.5% yield of the dienone.[55] Surber et al. studied the partial hydrogenation of enynone **18** and **15** in the presence of Pd–$CaCO_3$ in hexane under exclusion of light. However, the products of the hydrogenation at the uptake of 1 equiv of hydrogen appeared to be mixtures containing *trans*-ketones, cyclic enol ether (pyran), unchanged starting materials, and more saturated products than the dienones, as shown in eq 4.19 with **15**.[56] In either case, the *cis*-dienones could not be detected with certainty.



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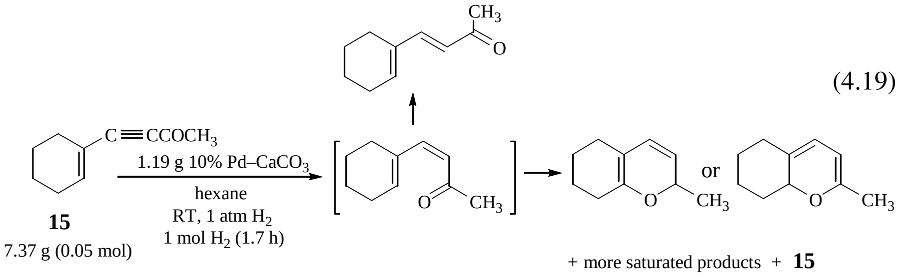

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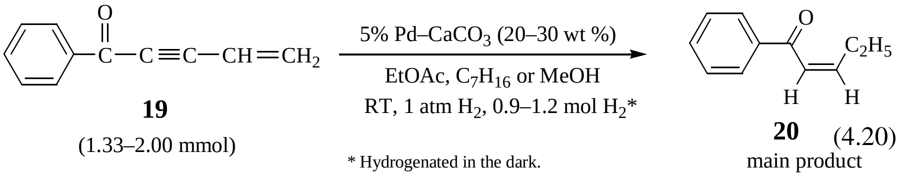

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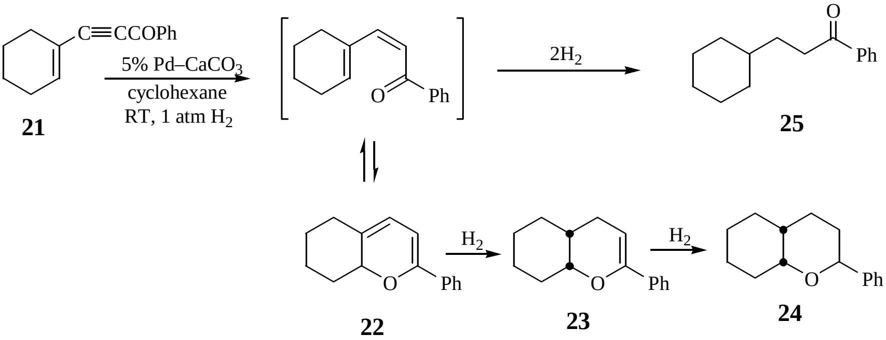


Scheme 4.2 Reaction sequence deduced from the products of semihydrogenation of 1-phenyl-3-(cyclohexen-1-yl)-2-propynone (**21**) over Pd catalyst.

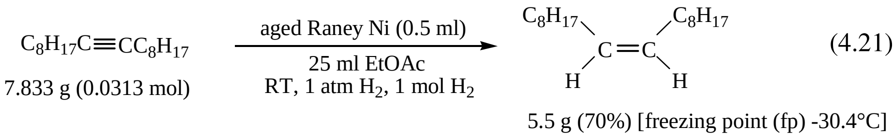
Marvell et al. found that the main product in the semihydrogenation of enynone **19** over Pd–$CaCO_3$ alone or with added zinc acetate or quinoline was *cis*-1-phenyl-2-penten-1-one (**20**), indicating that the terminal vinyl group was hydrogenated competitively with the triple bond (eq. 4.20).[57] Lindlar catalyst gave no better results. Similar semihydrogenation of enynone **21** gave a complex mixture that indicated the reaction sequence shown in Scheme 4.2. Evidence for the presence of the 2*H*-pyran **22** and the dihydropyran **23** was obtained, and saturated products **24** and **25** were isolated from the reaction mixture. The outcome of the hydrogenation was influenced to only small extent by the catalyst (Pd–$CaCO_3$ or Lindlar catalyst), the solvent (ethyl acetate or cyclohexane), and the presence or absence of quinoline.[57]

Besides the examples described above, many other palladium catalyst systems have also been described, mostly in patents, to be effective for partial hydrogenation of acetylenes. They include Pd–C–$Cu(OAc)_2$,[58,59] Pd–Al_2O_3–$Cu(OAc)_2$ with hydrazine hydrate,[59] and Pd–C- plus Pd–$CaCO_3$–$Zn(OAc)_2$–Et_2NH.[60]

4.2 HYDROGENATION OVER NICKEL CATALYSTS

Nickel catalysts have been employed successfully for the semihydrogenation of various acetylenic compounds.[1] Dupont was the first to study the hydrogenation of acetylenes using Raney Ni. Little or no change in the rate of hydrogenation on the uptake of 1 equiv of hydrogen was observed with the monosubstituted acetylenes, 1-heptyne

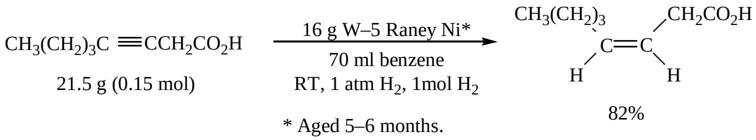
and phenylacetylene, in contrast to the disubstituted acetylenes, 2-octyne and 1-methoxy-2-nonyne.[61] Campbell and O'Connor made similar observations in the hydrogenation of various mono- and dialkylacetylenes, mono- and diphenylacetylenes, and phenylmethylacetylene over Raney Ni (W-1) in methanol at room temperature and an initial hydrogen pressure of 0.41 MPa.[62] Their results showed that a change in the rate of hydrogen uptake at half-hydrogenation was particularly noticeable in the case of the symmetric dialkylacetylenes. Phenylacetylene and phenylmethylacetylene showed no change in the rate at half-hydrogenation, while diphenylacetylene readily absorbed 1 equiv of hydrogen and the hydrogenation stopped at that point to yield *cis*-stilbene. The Raney Ni–catalyzed semihydrogenation was used by Campbell and Eby for the preparation of *cis* isomers of 3-hexene, 3- and 4-octenes, and 5-decene from the corresponding dialkylacetylenes.[63] The yields of the *cis*-olefins of constant boiling point, constant index of refraction were about 75–90%, although the *cis*-alkenes obtained by Campbell and Eby were later found not to be of high purity.[64,65] Elsner and Paul found that the Raney Ni that had been stored under ethanol for 6 months and became non-pyrophoric was much more selective than the freshly prepared one in the hydrogenation of isomeric octadecynes.[66] Except for 1- and 2-octadecynes, the rates in hydrogen uptake of isomeric octadecynes at the second stage fell to 3–10% of those at the initial. Further, a more selective Raney Ni was prepared by treating pyrophoric Raney Ni with ethanolic copper acetate so that up to 10% of copper was deposited on the nickel. Over the Cu-treated Raney Ni, the hydrogen uptake at the second stage was depressed almost completely except in the case of 1-octadecyne, where the hydrogenation did not halt after absorption of 1 mol of hydrogen, although the reaction slowed down significantly. The aged or Cu-treated Raney Ni was preferred to starch-supported colloidal palladium, quinoline-poisoned Pd–C, or Pd–$CaCO_3$ in pyridine, for the preparation of *cis*-octadecenes from hydrogenation of the corresponding octadecynes in both selectivity and activity. An example is shown in eq. 4.21.[66]



(4.21)

The Raney Ni catalyzed hydrogenation has often been applied to the synthesis of *cis*-olefinic fatty acids from the corresponding acetylenic acids.[67–69] Howton and Davis hydrogenated 5-octynoic acid over W-5 Raney Ni in ethanol at room temperature and atmospheric hydrogen pressure and obtained *cis*-5-octenoic acid in essentially quantitative yields, aside from mechanical losses, by discontinuing the hydrogenation when a sharp decrease in hydrogen uptake rate was noted; in the case of its methyl ester, however, no break in the hydrogen uptake rate was observed.[70] Khan prepared a Raney nickel catalyst that was selective in the hydrogenation and deuteration of the triple bond, by removing alkali and lighter catalyst particles containing alumina from W-1 Raney Ni through a continuous washing process.[71] The alkali-free catalyst was washed with dioxane and covered with dioxane, which was then distilled until the vapor reached 101°C. For deuteration, the catalyst was further treated with D_2O and then

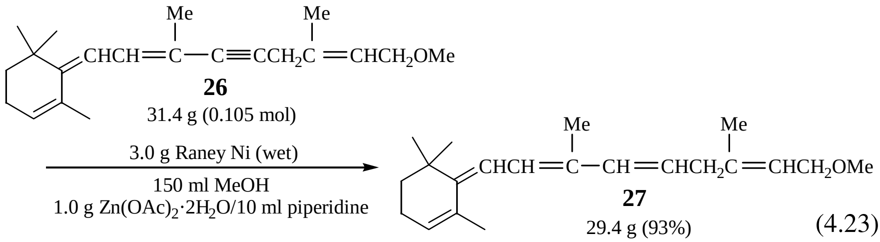
washed with dioxane. The Raney Ni catalyst thus prepared, denoted W-8, was found to be more selective than the Raney Ni such as W-1, W-2, and W-3. The deuteration of a symmetric acetylenic hydrocarbon, 9-octadecyne, over W-8 Raney Ni in dioxane stopped exactly after the reduction of the triple bond to the double bond, to give 9,10-dideuterooctadecene of 5.32 deuterium atom% (1.915 *d*). Such a high selectivity in the hydrogenation of a symmetric acetylenic hydrocarbon was also noted by other investigators.[62,65,72] The hydrogenation of stearolic acid and its methyl ester over W-8 Raney Ni fell down to an almost negligible rate after 1 equiv of hydrogen had been absorbed, while W-2 and W-3 catalysts tended further to saturate the double bond. In addition, the ester group of methyl stearolate was partly reduced over W-2 and W-3 catalysts. Deuteration of methyl stearolate over deuterized W-8 Raney Ni in dioxane at room temperature and atmospheric pressure, using 8–10% by wt of catalyst (wet by solvent), gave the crude products consisting of 2.9% methyl tetradeuterostearate, 2.5% methyl stearolate, and 94.6% methyl 9,10-dideuterooctadecenoate (94% *cis*, 6% *trans*). The crude product of the hydrogenation of stearolic acid over W-6 Raney Ni was found to consist of 72% of oleic (containing ~6% *trans*), 16% of stearolic, and 12% of stearic acid after 1 mol of hydrogen had been absorbed.[73] Knight and Diamond used the W-5 Raney Ni, which had been aged for 5–6 months in dry thiophene-free benzene, for the preparation of *cis*-3- (eq. 4.22), -4-, and -6-octenoic acids by the semihydrogenation of the corresponding octynoic acids.[74] The hydrogenations were interrupted after the theoretical quantity or slight excess of hydrogen had been taken up, since in no instance was a sharp break in the rate of hydrogenation observed. The *cis*-octenoic acids were thus obtained in 61–82% yields. Hofmann and Sax, however, obtained a *cis*-vaccenic acid (*cis*-11-octadecenoic acid) that was contaminated with large amounts of stearic acid in the hydrogenation of 11-octadecynoic acid over Raney Ni, and preferred the use of 5% Pd–C in ethanol containing 20% by volume of pyridine over which the hydrogenation ceased after the uptake of 1.09 equiv of hydrogen to yield an 88.4% yield of *cis*-vaccenic acid and 1.02% of stearic acid.[75]



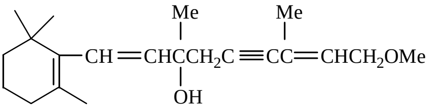
(4.22)

Oroshnik et al. used a Raney Ni poisoned with zinc acetate and piperidine in partial hydrogenation of acetylenic compounds with various conjugated enyne systems.[76–78] As an example, the rate of hydrogen absorption in the semihydrogenation of **26** with a conjugated trienyne system over the poisoned Raney Ni in methanol at room temperature and atmospheric pressure slowed down from 25 ml/min during the major part of the reaction to 2 ml/min at the end, and the product **27** with a conjugated tetraene system was obtained in more than 90% yield (eq. 4.23).[76] The same poisoned Raney Ni was also applied successfully to the semihydrogenation of compounds **28** and **29**, although no sharp change in hydrogen uptake was observed at the end. The results with these compounds were essentially the same as those obtained over the Lindlar

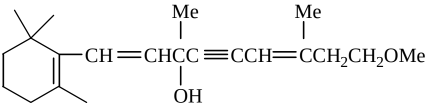
catalyst.[77] However, an advantage of the use of the poisoned Raney Ni was experienced in the hydrogenation of compounds **30** and **31** where no absorption of hydrogen occurred with Lindlar catalyst in either alcohol or isooctane.[78]



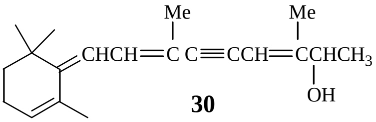
(4.23)



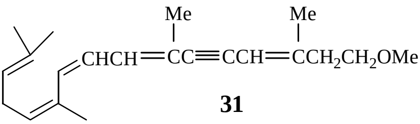
28



29

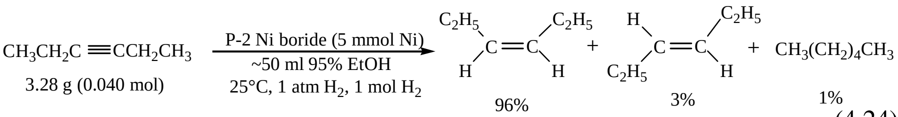


30



31

Brown and Ahuja found that, in contrast to the nickel boride prepared in an aqueous solution, denoted P-1 Ni, the nickel boride prepared by reduction of nickel acetate in ethanolic solution, denoted P-2 Ni, was highly selective in the hydrogenation of dienes and acetylenes.[79] Thus, over P-2 catalyst 3-hexyne was hydrogenated quantitatively to yield 3-hexene of a high *cis/trans* ratio (eq. 4.24). The P-2 catalyst, however, was not selective in the hydrogenation of 1-hexyne; at half-hydrogenation a mixture of hexane:1-hexene:1-hexyne in a ratio of 1:4:1 was formed (by GC analysis). The high selectivity of the P-2 catalyst over the P-1 catalyst may be related to the surface layer of oxidized boron species, which has been produced much more dominantly during the reduction of nickel salts with $NaBH_4$ in ethanol than in water.[80] The stereoselectivity of P-2 Ni in the formation of *cis*-alkenes from alkynes was further improved with addition of ethylenediamine, which was found to be effective among a series of amines investigated, including quinoline, pyridine, and piperidine (Table 4.3).[81]



(4.24)

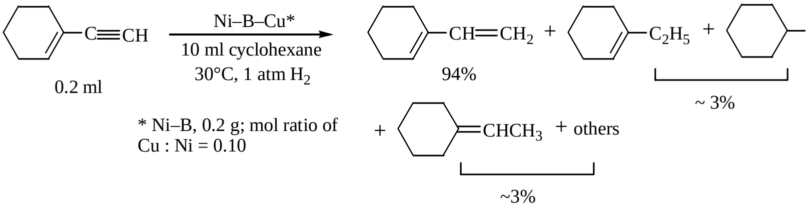
Nitta et al. compared the selectivity of copper, cobalt, and nickel borides (Cu–B, Co–B, and Ni–B) as well as Raney Ni and Ni–B modified with copper(II) chloride, in the partial hydrogenation of acetylenic compounds.[82] The selectivity at 30% conversion

TABLE 4.3 Stereoselective Hydrogenation of Disubstituted Alkynes over P-2 Ni in the Presence of Ethylenediamine[a,b]

Substrate (mmol)	P-2 Ni (mmol)	% Olefin[c]	*Cis*:*Trans* Ratio[c]	Total Yield of *cis*-Olefin (%)
3-Hexyne (40)	5.0	98	97:1	> 95[c]
3-Hexyne (200)	10.0	97	~ 200:1	> 95[c] (80)[d]
1-Phenylpropyne (100)	5.0	96	~ 200:1	> 95[c]
3-Hexyn-1-ol (40)	5.0	98	> 100:1	94[d]

[a]Data of Brown, C. A.; Ahuja, V. K. *J. Chem. Soc., Chem. Commun.* **1973**, 553. Reprinted with permission from Royal Society of Chemistry.
[b]To ethanolic suspension of P-2 Ni prepared in situ by borohydride reduction of $Ni(OAc)_2{\cdot}4H_2O$, was added ethylenediamine (2–3 times molar amounts of catalyst), followed by the substrate. Hydrogenations were carried out at 20–25°C and 1 atm H_2.
[c] GC analysis.
[d] Isolated yield.

as defined by mol% of alkene in alkene + alkane (given in parentheses) increased in the following order: Co–B (79.0) < Raney Ni (88.0) < P-1 Ni–B (90.0) < P-2 Ni–B (91.3) < Cu–B (92.0) < Cu-modified Raney Ni (93.2) < Cu-modified P-1 Ni–B (98.3), in the hydrogenation of phenylacetylene in ethanol at 30°C and 1 atm H_2. The selectivities of the catalysts were almost independent of the conversion of acetylenes up to 90%. Thus, treatment of Raney Ni and Ni–B with copper(II) chloride improved their selectivities significantly, while the selectivity of Ni–B was improved only slightly with zinc or iron(II) salts. The selectivity in the hydrogenation of 1-heptyne, 1-ethynylcyclohexene, and propargyl alcohol over the Cu-modified Ni–B, which showed the highest selectivity of the catalysts investigated, was 89.7, 94, and 80.3%, respectively. Hydrogenation of 1-ethynylcyclohexene over the Cu-modified Ni–B in cyclohexane did not proceed further after all ethynylcyclohexene had been consumed. Vinylcyclohexene was formed in 94% yield, together with 6% of monoolefins, but no ethylcyclohexane was found in the product (eq. 4.25).



(4.25)

Brunet et al. studied selective semihydrogenation of acetylenes over a nickel catalyst, denoted Nic, which was obtained from a mixture of NaH–*t*-PeOH–$Ni(OAc)_2$ in THF

at 45°C.[83,84] Hydrogenations were carried out in methanol or ethanol usually in the presence of quinoline at 25°C and 1 atm H_2. The presence of quinoline allowed one to more easily obtain the maximum yields of semihydrogenation products and also depressed dramatically *cis–trans* isomerization. Hydrogenations were stopped just after the uptake of 1 equiv of hydrogen for disubstituted acetylenes and after the uptake of 1.2 equiv of hydrogen for 1-alkynes. Under these conditions hydrogenation of phenylacetylene over Nic gave styrene of 91% purity in 90% isolated yield and hydrogenation of 3-hexyne over the Nic washed with ethanol (Nic_w) afforded *cis*-3-hexene of 97% purity in 80% isolated yield. 1-Ethynylcyclohexene was hydrogenated to give 1-vinylcyclohexene of 80% purity in 84% isolated yield; the results apparently were comparable to those obtained with Lindlar catalyst (cf. eqs. 4.6 and 4.25).

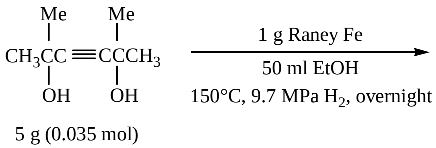
Savoia et al. prepared a highly dispersed nickel-on-graphite catalyst, denoted Ni–Gr1, by reduction of $NiBr_2{\cdot}2DME$ (1,2-dimethoxyethane) in THF-HMPTA solution with C_8K (potassium graphite). Freshly prepared Ni–Gr1 was found to be highly selective when used in situ for semihydrogenation of alkynes in the presence of ethylenediamine.[85] Hydrogen uptake slowed down to about one-fifth of the previous rate for terminal and conjugated alkynes, while virtually ceased with other nonconjugated ones. Hydrogenation of 1-decyne over Ni–Gr1 in THF gave a mixture of 13% of decane, 75% of 1-decene, and 12% of 1-decyne, while 5-decene of a high *cis/trans* ratio was obtained in 98% yield in hydrogenation of 5-decyne (GC analysis) (eq. 4.26).

$$\underset{0.73\text{ g (5.3 mmol)}}{C_4H_9C{\equiv}CC_4H_9} \xrightarrow[\substack{\text{THF/0.5 ml EDA} \\ 25^\circ\text{C, 1 atm } H_2\text{, 99.5\% conversion}}]{\text{Ni–Gr1 (0.2 mmol Ni)}} \underset{\substack{98\% \\ (Z/E = 98.9/1.1)}}{C_4H_9CH{=}CHC_4H_9} + \underset{1.5\%}{\text{decane}} \qquad (4.26)$$

Mauret and Alphonse reported that a finely divided nickel prepared by reduction of nickel halide with magnesium in ethanol was more selective for semihydrogenation of both mono- and disubstituted acetylenes than Raney Ni or those obtained by reduction in THF.[86] With the nickel produced in ethanol, the rate of hydrogen uptake after 1 equiv was almost nil in the case of 3-hexyne, and 98–99% of *cis*-3-hexene along with only 1–2% of hexane was produced.

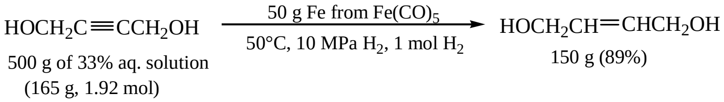
4.3 HYDROGENATION OVER IRON CATALYSTS

Paul and Hilly reported that Raney Fe, which was inert for the hydrogenation of olefins, was effective for the semihydrogenation of acetylenes.[87] The absorption of hydrogen ceased spontaneously after the uptake of 1 equiv. Thus, over Raney Fe, hydrogenations of 1-heptyne (135°C and 5.2 MPa H_2) and 1-octyne (100°C and 6.2 MPa H_2) afforded the corresponding 1-alkenes in 90 and 85% yields, respectively. Thompson, Jr. and Wyatt also studied the use of Raney Fe in the partial hydrogenation of acetylenes.[88] Although diphenylacetylene was hydrogenated to diphenylethane at 100°C and 6.9 MPa H_2, 2,5-dimethyl-3-hexyne-2,5-diol was hydrogenated nearly quantitatively to the corresponding olefin at 150°C and 9.7 MPa H_2 (eq. 4.27).



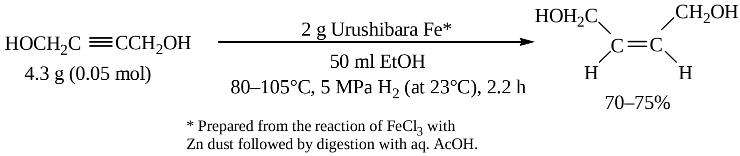
(4.27)

2-Methyl-1-buten-3-yne, a conjugated enyne, was also hydrogenated to give the product containing at least 50% of diene (isoprene) even after an 18-h reaction at 100°C and 6.9 MPa H_2. Reppe et al. hydrogenated 2-butyne-1,4-diol over an iron catalyst, prepared by decomposition of pentacarbonyliron, in water at 50°C and 10 MPa H_2 and obtained 2-butene-1,4-diol in ~90% yield, by interrupting the reaction at the uptake of hydrogen corresponding to 1 equiv (eq. 4.28).[41] Over Raney Fe, up to 80% yield of the butenediol was obtained similarly by interrupting the hydrogenation after the uptake of ~1.1 equiv of hydrogen. With higher alkynediols, however, the hydrogenation over iron catalyst proceeded only to produce the alkenediols. For example, 3-hexyne-2,5-diol was hydrogenated practically quantitatively to 3-hexene-2,5-diol at 100°C and 20 MPa H_2.



(4.28)

Taira hydrogenated 2-butyne-1,4-diol using Urushibara Fe as catalyst in ethanol at 80–100°C and an initial hydrogen pressure of 5–7 MPa until the hydrogen uptake ceased and obtained *cis*-2-butene-1,4-diol in 70–75% yield (eq. 4.29).[89]



(4.29)

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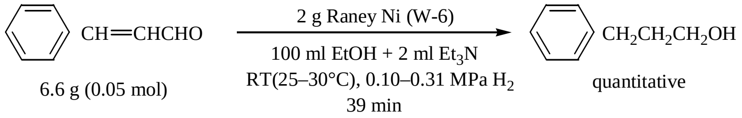
CHAPTER 5

Hydrogenation of Aldehydes and Ketones

Aldehydes and ketones are usually easily hydrogenated to the corresponding alcohols over most of the transition metal catalysts. The rates of hydrogenation of carbonyl compounds, however, depend on the nature of catalysts; the structure of compounds, such as aliphatic or aromatic and hindered or unhindered; the reaction medium; as well as the reaction conditions. Acidic, alkaline, or other additives or the impurities associated with catalyst preparation may greatly influence the rates of hydrogenation and in some cases the product selectivity and stereoselectivity. Hydrogenations of alcohols produced to give hydrocarbons seldom take place under mild conditions except with arylic aldehydes and ketones of ArCHOHR type, where the benzyl-type alcohols formed are further susceptible to hydrogenolysis to give the corresponding methylene compounds $ArCH_2R$. Direct hydrogenation of the carbonyl group to the methylene may occur over some platinum metals especially under acidic conditions. In most cases, however, the reaction occurs only to minor extents or not at all, and the hydrogenation to give the alcohol is by far the major reaction. The hydrogenation of carbonyl compounds over some platinum metals in alcoholic solvents, in particular in primary alcohols, under acidic conditions or with a catalyst of acidic nature may be accompanied by the formation of acetals, which often lowers the rate of hydrogenation and may lead to the formation of ethers.

5.1 ALDEHYDES

Aldehydes are readily hydrogenated to the corresponding alcohols over nickel and copper–chromium oxide catalysts.[1] In general, Raney Ni, especially highly active ones such as W-6,[2] are preferred to other nickel catalysts for the hydrogenations at low temperatures and pressures. Raney Ni may further be promoted by the addition of triethylamine[2] or triethylamine and a small amount of chloroplatinic acid,[3,4] as shown in eqs. 5.1 and 5.2.



(5.1)

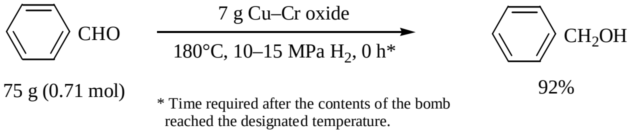
$$\underset{8.6\text{ g (0.10 mol)}}{(CH_3)_2CHCH_2CHO} \xrightarrow[\text{100 ml EtOH + 2 ml Et}_3\text{N + 0.22 mmol PtCl}_4 \text{; RT, 0.31 MPa H}_2\text{, 28 min}]{\text{3 g wet Raney Ni (W-6)}} \underset{91\%}{(CH_3)_2CHCH_2CH_2OH} \quad (5.2)$$

For more effective and/or larger-scale hydrogenations, use of higher temperatures and pressures is advantageous as in an example shown in eq. 5.3.[5] Supported nickel catalysts such as Ni–kieselguhr may also be useful at temperatures above 100°C (eq. 5.4).[6]

$$\underset{\text{408 g (4 mol)}}{CH_3OCH_2CH(CH_3)CHO} \xrightarrow[\text{80–100°C, 10.3 MPa } H_2\text{, 0.5 h}]{\text{20 g Raney Ni}} \underset{\text{389 g (93.5\%)}}{CH_3OCH_2CH(CH_3)CH_2OH} \quad (5.3)$$

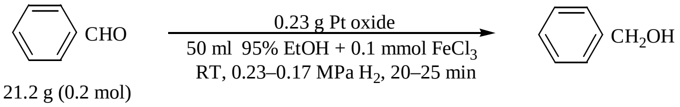
$$\underset{\text{88 g (1 mol)}}{CH_3CHOHCH_2CHO} \xrightarrow[\text{125°C, 17 MPa } H_2\text{, 1 h}]{\text{2 g Ni–kieselguhr}} \underset{\text{39\%}}{CH_3CHOHCH_2CH_2OH} \quad (5.4)$$

Copper–chromium oxide catalyst is effective for the hydrogenation of aldehydes at a temperature of 125–150°C.[1] The hydrogenation of benzaldehyde over copper–chromium gives a high yield of benzyl alcohol even at 180°C without hydrogenolysis to give toluene (eq. 5.5).[7]



(5.5)

With platinum catalysts aldehydes have often been found to be difficult to reduce.[8–10] Faillebin found that pure platinum black, prepared by reduction of chloroplatinic acid with formalin and alkali, was a very poor catalyst for the hydrogenation of aldehydes and tended to give hydrocarbons, while aldehydes were reduced to alcohols in excellent or quantitative yield over the catalyst prepared from a mixture of chloroplatinic acid and 5% of ferric chloride.[9] Adams platinum oxide catalyst becomes inactive very quickly during the hydrogenation of aldehydes in 95% ethanol; only by frequent reactivation with air can the hydrogenation be carried to completion. However, when small amounts of ferrous or ferric chloride were added, hydrogenation of benzaldehyde went rapidly to completion without any reactivation with air (eq. 5.6).[10] It has been shown that ferric chloride is first reduced to ferrous chloride and becomes as effective as ferrous chloride. The hydrogenation of heptanal was similarly accelerated markedly by the addition of ferrous chloride (eq. 5.7). Dilute alcohol was used as solvent for heptanal, since, on adding even very small amounts of ferrous chloride to solutions of heptanal in 95% ethanol, heat was evolved with acetal formation accompanied by polymerization. In the absence of ferrous chloride it was possible to hydrogenate the aldehyde only by repeated activation of the catalyst. The effect of ferrous chloride was interpreted to inhibit an aldehyde to rob the catalyst of the oxygen that was necessary for its activity.[11]



(5.6)

$$\underset{22.8\ \text{g (0.2 mol)}}{CH_3(CH_2)_5CHO} \xrightarrow[\substack{65\ \text{ml 95\% EtOH–40 ml}\ H_2O + 0.1\ \text{mmol}\ FeCl_2 \\ \text{RT, 0.23–0.17 MPa}\ H_2,\ \text{25–30 min}}]{0.23\ \text{g Pt oxide}} CH_3(CH_2)_5CH_2OH \qquad (5.7)$$

Maxted and Akhtar studied the effect of the addition of various metal chlorides in the hydrogenation of valeraldehyde with platinum oxide in ethanol at 20°C and atmospheric pressure.[12] The effect of a constant small amount (10^{-5} mol) of metal chlorides on the hydrogenation rate of valeraldehyde (1 ml) in ethanol (9 ml) with 0.025 g of platinum oxide as indicated by the amount of hydrogen absorbed (ml) in 1 h (see figures in parentheses) was in the following order: $SnCl_2$ (127) > $FeCl_3$ (92) > $CoCl_2$ (69) > $SnCl_4$ (53) > $CeCl_3$ (38) > $ZnCl_2$ (34) > $CrCl_3$ (29) > $CuCl_2$ (27.5) > $MnCl_2$ (25) > $AlCl_3$ (23.5) > none (12). Thus stannous chloride has been shown to be the most effective promoter of the metal chlorides tested, and an increase in rate of at least 10 times its unpromoted value has been obtained with the addition of salt prior to reduction of the platinum oxide to metal. On the other hand, prereduced platinum black was poisoned with both stannous chloride and ferric chloride, as observed in the hydrogenation of cyclohexene. Since the promoters used were in all cases very small quantities of metal salts known to be toxic in catalytic hydrogenation on platinum, Maxted and Akhtar assumed that the promoting action takes place by retarding the autocatalytic reduction of the platinum oxide to metal in such a way as to prolong the period during which highly active nascent platinum is being produced.

The promoting effect of stannous chloride has also been observed with supported platinum and ruthenium catalysts in the hydrogenation of heptanal.[13] The effect of stannous chloride on ruthenium catalysts, however, has been considered to primarily eliminate the induction period, since no effect on rate was observed when a freshly prepared ruthenium catalyst, which had no induction period, was used. The overall activity of supported platinum and ruthenium catalysts has also been improved by periodic shaking with air similarly with unsupported platinum catalysts. The reactivation by shaking with air may be attributed to flushing out of catalyst poisons, possibly carbon monoxide,[14,15] although shaking with nitrogen, instead of air, did not change the catalyst activity at all.[13] An example showing the effectiveness of ruthenium catalyst for the hydrogenation of an aliphatic aldehyde is as follows:[16]

$$\underset{22.8\ \text{g (0.2 mol)}}{CH_3(CH_2)_5CHO} \xrightarrow[\substack{150\ \text{ml 60–80\% aq. EtOH} \\ \text{RT, 0.3 MPa}\ H_2,\ \text{5–6 h}}]{2.5\ \text{g 5\% Ru–C*}} \underset{\text{quantitative}}{CH_3(CH_2)_5CH_2OH} \qquad (5.8)$$

* Prereduced for 1 h in 50 ml 80% EtOH

Hydrogenation of aldoses to alditols (polyhydric alcohols) is usually performed in an aqueous solution with nickel or ruthenium as catalyst, as seen in the examples shown in eqs. 5.9–5.11.[17–19]

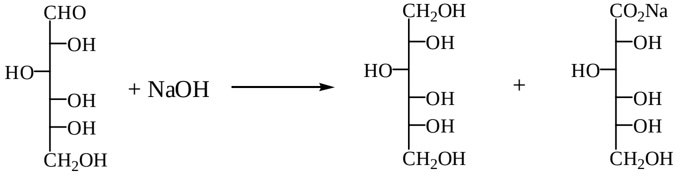
$$\underset{3.0\ \text{g}}{\text{D-Rhamnose hydrate}} \xrightarrow[\substack{50\ \text{ml}\ H_2O \\ 100°\text{C, 10 MPa}\ H_2,\ \text{5 h}}]{0.6\ \text{g Raney Ni}} \underset{2.7\ \text{g (100\%)}}{\text{D-rhamnitol}} \qquad (5.9)$$

$$\underset{20\text{ g }(0.11\text{ mol})}{\text{D-Glucose}} \xrightarrow[\substack{35\text{ ml } H_2O \\ 150°\text{C, } 17.2\text{ MPa } H_2\text{, } 2.5\text{ h}}]{2\text{ g Ni–kieselguhr}} \underset{97\%}{\text{sorbitol}} \tag{5.10}$$

$$\underset{18\text{ g }(0.1\text{ mol})}{\text{D-Glucose}} \xrightarrow[\substack{50\%\text{ aq. solution} \\ 140°\text{C, } 10\text{ MPa } H_2\text{, } 20\text{ min}}]{0.1\text{ g Ru}} \underset{95\%}{\text{sorbitol}} \tag{5.11}$$

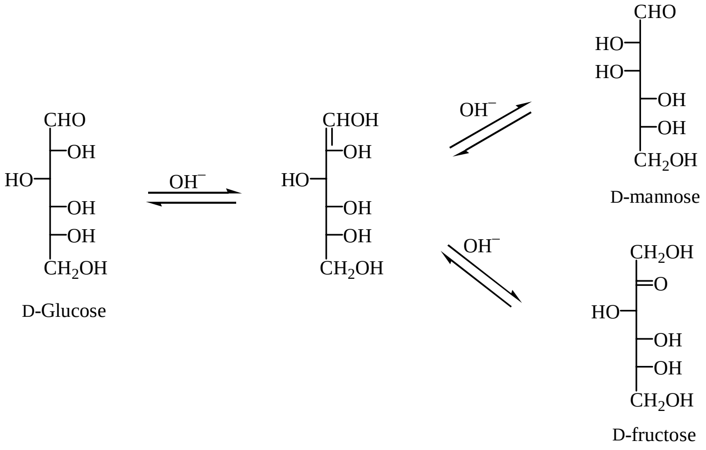
The manufacture of sugar alcohols such as sorbitol, mannitol, and xylitol has been an industrially important process, and many patents and articles may be found in the literature. Of these polyhydric alcohols, sorbitol is by far the most important and is manufactured in largest scale, since it finds numerous applications in various fields such as vitamin C production, cosmetics and dentifrices, foods and semiluxuries, surfactants and adhesives, pharmaceuticals, and many other miscellaneous uses. For an excellent article on the production of sugar alcohols by catalytic hydrogenation and their applications, see Albert et al.[20] In an industrial process described by Fedor et al., a deionized aqueous solution of dextrose was hydrogenated over Raney Ni.[21] The hydrogenation was completed within 3 h at 6.9 MPa H_2 and the temperature controlled below 150°C during the reaction. In a hydrogenation of a 20% ethanol solution of glucose over 5.3–26.5% Ni–Al_2O_3 catalysts at 50–150°C and 5–6 MPa H_2, the optimal reaction temperature was 120°C, because the hydrogenation was slow below this temperature and at higher temperature marked decomposition and caramelization took place.[22] The rate of hydrogenation of D-glucose is increased in alkaline solution, but these conditions also promote a Cannizzaro type of disproportionation giving D-glucitol and D-gluconic acid (Scheme 5.1). To avoid this side reaction, the hydrogenation in the presence of anion-exchange resins of appropriate basicity was reported to be effective in rapid hydrogenation and the depression of the disproportionation.[23]

Ishikawa[24] studied the activity of Raney nickel catalysts promoted by various metals, prepared from Raney aluminum–nickel–metal ternary alloys, in the hydrogenation of glucose in water at 125°C and initial hydrogen pressure of 6 MPa. The maximum activities on the basis of unit surface area, which were much greater than with unpromoted Raney Ni, were obtained by the addition of 15–20 atom% of tin, molybdenum, iron, and manganese to the nickel in the alloy. In a discontinuous suspension batch process described by Albert et al., D-glucose was hydrogenated in 50% aqueous solution over a Raney nickel catalyst promoted by molybdenum at 110°C and



D-Glucose sorbitol (D-glucitol) D-gluconic acid

Scheme 5.1 Cannizzaro reaction of D-glucose.



Scheme 5.2 Lobry de Bruyn–van Ekenstein transformation of D-glucose.

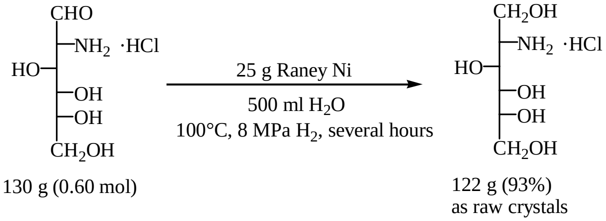
5 MPa H_2. To suppress the isomerization of D-glucose to D-mannose and D-fructose (Lobry de Bruyn–van Ekenstein transformation) (Scheme 5.2) and the Cannizzaro reaction, which were both promoted in an alkaline medium, the pH value was maintained between 5.5 and 6.5. Under the conditions that were optimized to minimize the side reactions, the formation of gluconic acid and mannitol was reduced to less than 1% each at 99.5–99.6% conversion, while with a normal nonpromoted Raney Ni 1.5–2.1% of gluconic acid and 1.3–1.9% of mannitol were formed at 99.5–99.7% conversion.

In a continuous suspension process using a supported nickel catalyst such as Ni–kieselguhr, D-glucose was hydrogenated at a pH of approximately 5.0 at 140°C and 17 MPa H_2 to give 95–96% yields of sorbitol at 99.0–99.5% conversion.[20] Cerino et al. studied the activity and stability of Raney nickel catalysts promoted with molybdenum, chromium, and iron,[25] which are known to promote the hydrogenation of glucose.[26] Before hydrogenation at 130°C and 4.5 MPa H_2, the pH of a D-glucose solution (3.37 $mol \cdot l^{-1}$) was adjusted at 6.5 with acetic acid. Although iron produced the largest rate enhancement, the catalytic activity markedly decreased with successive recyclings. It has been suggested that this decrease in the rate is caused by leaching of the iron atoms from the surface, as shown by the decrease in Fe/Ni ratio before and after five hydrogenation cycles. The presence of molybdenum and chromium on the nickel surface has been found to be beneficial for the stability of catalytic activity since they decrease side-cracking reactions, which produce the organic fragments poisoning the catalyst.

The use of ruthenium or ruthenium-based catalysts in the production of polyhydric alcohols by hydrogenation of aldoses or by simultaneous hydrolysis and hydrogenation of polysaccharides has been the subject of a considerable body of investigations.[20,27] Ru–C was used in the hydrogenation of dextrose to sorbitol in both continuous and batch processing at elevated temperatures (100–180°C) and hydrogen

pressures (3.4–13.8 MPa).[28] Ruthenium catalysts promoted by palladium have also been used for the hydrogenation of glucose to sorbitol. In one example, 35 g of D-glucose was hydrogenated over 1.6% Ru/3.4% Pd–C in 65 g water at 126°C and 6.9 MPa H_2 to yield a product containing 97.95% of sorbitol.[29] Arena studied the deactivation of ruthenium catalysts in a continuous glucose hydrogenation.[30] The accumulation of iron, sulfur, and gluconic acid on the catalyst was detected. When iron and gluconic acid poisoning was minimized, substantial improvements in catalyst stability were achieved.

D-Glucosamine was hydrogenated to D-glucosaminitol (2-amino-2-deoxyglucitol) with nickel catalyst as its acetyl derivative[31] or hydrochloride (eq. 5.12).[31,32] The end residues of chitooligosaccharides, the oligomers of β-1,4-linked D-glucosamine with a degree of polymerization of 2–6, have been successfully hydrogenated to chitooligosaccharide–alditols with a ruthenium black as catalyst in water at 100°C and 6 MPa H_2 in the presence of a small amount of sodium acetate.[33] The instability of the chitooligosaccharides has been greatly improved by this hydrogenation. The presence of an alkaline substance was necessary to depress the coloration of the product that had been found as a result of dissolution of a slight amount of the ruthenium catalyst probably by a complex formation with the alditols.



(5.12)

The hydrogenation of Mannich bases of the formula **I** to the corresponding amino alcohols of formula **II** (in eq. 5.13) proceeded smoothly and in high yields when the hydrochlorides of **I** were hydrogenated with Raney Ni in aqueous solution of pH 3–6 (eq. 5.13).[34] Over noble metal catalysts only poor yields of the alcohols resulted. Hydrogenation of the free amines was even less satisfactory, regardless of whether noble metals or nickel were used. Leonard and Simet, however, hydrogenated 3-diethylamino-2,2-dimethylpropionaldehyde (**I**, R = Et) and 2,2-dimethyl-3-(1-piperidyl)propionaldehyde (**I**, R_2N = 1-piperidyl), dissolved in one-half their volume of ethanol, in the presence of Raney Ni, and obtained, respectively, 86 and 92% yields of the corresponding basic alcohols.[35] The hydrogenations were complete in 4.5–5 h when the temperature was gradually raised to 70–80°C at the initial hydrogen pressure of 12.4 MPa.

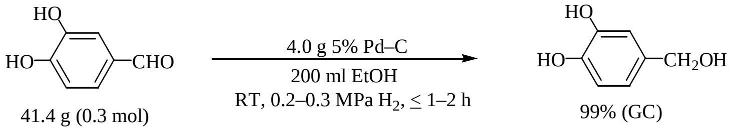
I **II**

$$(C_4H_9)_2NCH_2C(CH_3)_2CHO \xrightarrow[\substack{3M\ \text{aq. HCl*} \\ 60\text{–}70°C,\ 2.76\ \text{MPa}\ H_2,\ 2\ \text{h}}]{3\ \text{g Raney Ni}} (C_4H_9)_2NCH_2C(CH_3)_2CH_2OH \quad (5.13)$$

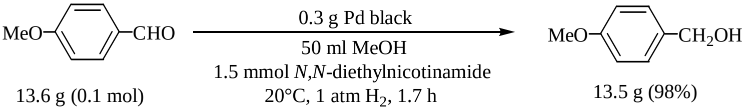
18.5 g (0.087 mol) → 12–13 g (64–70%)

* The pH was adjusted to 4–4.5 with NH_3.

Palladium catalysts are usually not active for the hydrogenation of aliphatic aldehydes. However, palladium is among the most active metals for the hydrogenation of aromatic aldehydes under mild conditions, although there is a report that benzaldehyde was not hydrogenated over borohydride-reduced palladium in methanol.[36] The rates of hydrogenation at atmospheric pressure and room temperature of benzaldehyde, furfural, salicylaldehyde, and *o*-chlorobenzaldehyde were greater over Pd–C than over Pt–C, Rh–C, and Ru–C.[37] Over 5% Pd–C, the rate of hydrogenation of benzaldehyde to benzyl alcohol decreased with solvent in the following order: AcOH > MeOH > EtOAc > hexane > DMF > benzene > H_2O. Although in benzene, hexane, ethyl acetate, and dimethylformamide the rate declined abruptly to a low value after absorption of 1 equiv of hydrogen, absorption of the second equivalent of hydrogen continued at a lower but still appreciable rate in methanol and acetic acid. Therefore, in methanol and acetic acid, high yields of benzyl alcohol could be obtained only by interrupting the hydrogenation after absorption of 1 equiv. Overreduction to the methyl group may also be avoided by employing a moderate amount of catalyst in neutral solvent (eq. 5.14)[38] or by hydrogenating in the presence of an inhibitor (eq. 5.15).[39]



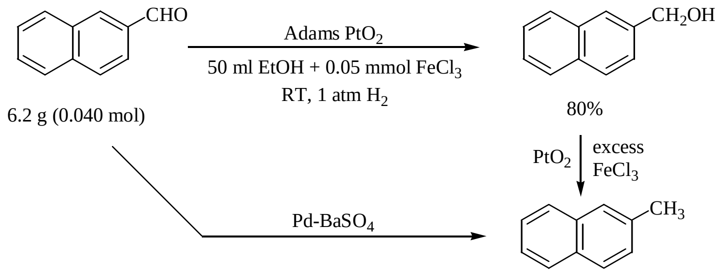
(5.14)



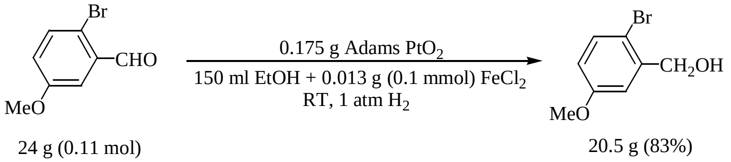
(5.15)

Platinum catalysts appear less prone to the overreduction of aromatic aldehydes, although a promoter such as ferrous or ferric chloride may often be required.[9,10,40,41] Thus, benzaldehyde (eq. 5.6) and 2-naphthalenecarbaldehyde (eq. 5.16)[40] were hydrogenated to benzyl alcohol and 2-naphthalenemethanol, respectively, in high yields over platinum catalysts in the presence of ferric chloride. With excess ferric chloride, however, overreduction of naphthenecarbaldehyde (probably to 2-methylnaphthalene) occurred. It should be noted that in the absence of the ferric salt benzaldehyde was reduced to give toluene[9] and over Pd–$BaSO_4$, 2-naphthalenecarbaldehyde was reduced to give 2-methylnaphthalene (see eq. 5.16).[40] Furfural could likewise be hydrogenated to furfuryl alcohol quantitatively over Adams platinum oxide and iron salt in ethanol by interrupting the reaction after absorption of 1 mol of hydrogen. Under similar conditions 2-bromo-5-methoxybenzaldehyde was hydrogenated until absorption of hydrogen ceased and the corresponding benzyl alcohol was obtained in

83% yield. Both overreduction and loss of bromine were depressed to low levels (eq. 5.17).[41]

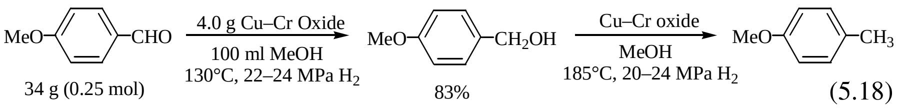


(5.16)



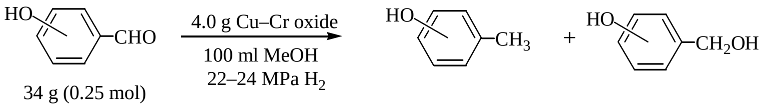
(5.17)

The overhydrogenation of aromatic aldehydes beyond benzylic alcohols is rarely important with copper–chromium oxide and Raney nickel unless the reaction conditions are too vigorous. Thus, over copper–chromium oxide *o*- and *p*-methoxybenzaldehydes were hydrogenated to the corresponding methoxybenzyl alcohols in high yields in methanol at 110–125°C and 22–24 MPa H_2 (eq. 5.18).[42] At 185°C, however, *p*-methoxybenzyl alcohol was hydrogenolyzed to give *p*-cresol methyl ether (eq. 5.18).



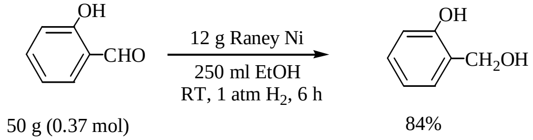
(5.18)

Both *o*- and *p*-hydroxybenzaldehydes were very susceptible to overreduction. The hydrogenation of these aldehydes over copper–chromium oxide at 110–130°C gave the corresponding cresols, while *m*-hydroxybenzaldehyde was reduced to *m*-hydroxybenzyl alcohol in 84% yield in the hydrogenation at 110–125°C (eq. 5.19).[42] Both *o*- and *p*-hydroxybenzaldehydes were successfully hydrogenated to the corresponding benzyl alcohols in the hydrogenation with Raney Ni in ethanol at room temperature and atmospheric pressure as shown in eq. 5.20 for the *ortho* isomer.[43] In water at room temperature and atmospheric pressure *o*-hydroxybenzaldehyde was hydrogenated only very slowly and the reaction became scarcely more rapid at 50–60°C. The aldehyde was hydrogenated rapidly at 55°C and 1.5–5.5 MPaH_2, but to give *o*-cresol.



(5.19)

HO: *ortho*	123–135°C, 2.3 h	86%	
: *para*	110–125°C, 1.5 h	73%	8%
: *meta*	110–125°C, 2.0 h	4%	84%

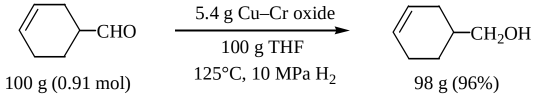


(5.20)

For depressing the overhydrogenation of aromatic aldehydes and ketones over nickel or copper–chromium oxide at elevated temperatures and pressures, the presence of an aqueous alkali metal carbonate or hydroxide is effective.[44] Thus, 60 g of benzaldehyde was hydrogenated over 1.5 g of a supported nickel in the presence of 2 ml of 10% aqueous sodium carbonate at 90–115°C and 3.2 MPa H_2 to give 91.5% of benzyl alcohol and 7.7% of toluene, compared to 48.7 and 49.5%, respectively, without aqueous sodium carbonate.

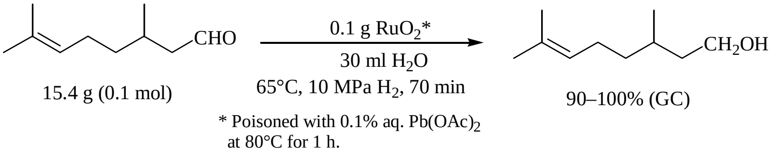
5.2 HYDROGENATION OF UNSATURATED ALDEHYDES TO UNSATURATED ALCOHOLS

Usually, unsaturated aldehydes in which the C–C double bonds are not conjugated with the C–O double bonds are preferentially hydrogenated to saturated aldehydes and alcohols unless the C–C double bonds are highly hindered. Over copper–chromium oxide, however, 3-cyclohexenecarboxaldehyde is selectively hydrogenated to the corresponding unsaturated alcohol (eq. 5.21).[45]



(5.21)

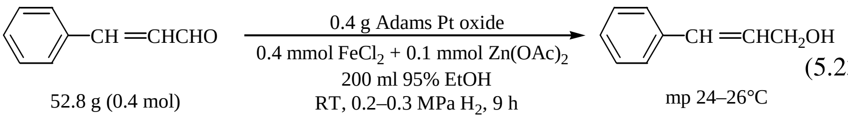
Citronellal, an aldehyde with a trisubstituted double bond, was hydrogenated to citronellol over a ruthenium catalyst poisoned with lead acetate in 90–100% yields (eq. 5.22)[46] or over chromium-promoted Raney Ni in 94% yield in methanol at 75°C and about 0.31 MPa H_2.[47] Court et al. studied the selective hydrogenation of citral (**1**, eq. 5.24) to citronellol over unsupported $Ni_{1-x}Mo_x$ catalysts, prepared by reduction of mixtures of metal iodides with naphthalene-sodium as reducing agent, in cyclohexane and in 2-propanol at 80°C and 1.0 MPa H_2.[48] Higher yields of citronellol were obtained in 2-propanol than in cyclohexane, primarily via citronellal as the predominant intermediate. The yields of citronellol for the overall hydrogenation in 2-propanol over Mo-promoted catalysts were $Mo_{0.03}$ 96%, $Mo_{0.06}$ 98%, and $Mo_{0.12}$ 96%.



(5.22)

α,β-Unsaturated aldehydes may be hydrogenated to the corresponding unsaturated alcohols by selecting appropriate catalysts and reaction conditions. The selectivity to unsaturated alcohols depends on various factors such as the structure of aldehyde, the nature of catalyst, and the presence of additive, as well as other reaction conditions. The selectivity in the hydrogenation of α,β-unsaturated aldehydes, therefore, has been a subject of many investigations using various catalysts or catalyst systems.[49] Probably acrolein is the most difficult of the α,β-unsaturated aldehydes to hydrogenate selectively to the allylic alcohols. The selective hydrogenation may take place more easily with crotonaldehyde because of the catalyst hindrance of the methyl group on the double bond to its adsorption. For the same reason 3-methylcrotonaldehyde and citral are expected to be hydrogenated more easily to the allylic alcohols than crotonaldehyde. Cinnamaldehyde, with an α,β-unsaturated aldehyde system conjugated with a phenyl group, appears to be much more selectively hydrogenated to cinnamyl alcohol than aliphatic unsaturated aldehydes.

Cinnamaldehyde and citral were selectively hydrogenated to cinnamyl alcohol[50] and geraniol,[51] respectively, over Adams platinum oxide in the presence of small amounts of iron and/or zinc salts, which were known to be efficient promoters for the hydrogenation of aldehydes.[10] In the presence of both ferrous chloride and zinc acetate in proper proportions, cinnamaldehyde was hydrogenated to pure cinnamyl alcohol, with no more than 1 equiv of hydrogen absorbed (eq. 5.23).[50] The platinum oxide had been reduced to platinum black before the substrate and the salts were added. In order to get uniform results, it is claimed that the oxide should be completely reduced before the aldehyde is added. If the oxide is reduced in the presence of the aldehyde, a platinum black of different activity results and requires more poisoning in the form of salts. With the catalyst made in this way, conditions were not found whereby the hydrogenation would stop after the absorption of 1 equiv of hydrogen, although it was possible to obtain a very good grade of cinnamyl alcohol by working up the reaction mixture after the hydrogen uptake of 1 equiv.[50]

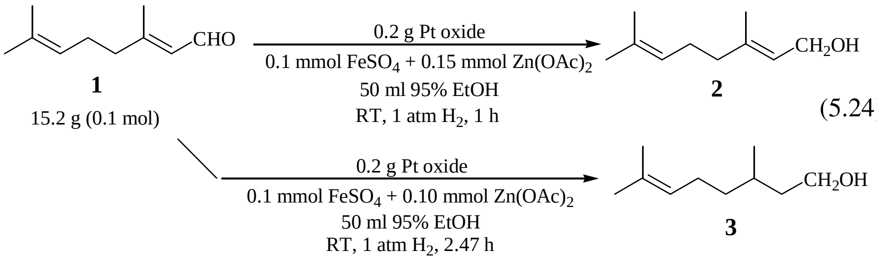


(5.23)

Blackmond et al. compared the selectivities of ruthenium, platinum, and rhodium supported on NaY and KY zeolites with those supported on carbon, in the hydrogenation of cinnamaldehyde and 3-methylcrotonaldehyde in isopropyl alcohol at 100°C (for rhodium and ruthenium) or 70°C (for platinum) and 4 MPa H_2.[52] Good selectivities to unsaturated alcohols were obtained over zeolite-supported ruthenium and platinum with

cinnamaldehyde (60–68% at 25% conversion) and over zeolite-supported platinum with 3-methylcrotonaldehyde (42–56% at 25% conversion). The results have been discussed in terms of geometric/steric and electronic effects that depended on the substrate hydrogenated. Augustine and Meng studied the effects of a number of metal salts in the hydrogenation of crotonaldehyde and cinnamaldehyde over 5% Pt–C in ethanol at 25–40°C and 1–3 atm of hydrogen.[49] The best selectivity was obtained by treating the platinum catalyst with solutions of iron salts prior to use in the hydrogenation (79% at 60% conversion with crotonaldehyde and 95% at 65% conversion with cinnamaldehyde at 40°C and 0.3 MPa H_2). With ferrous chloride there was more decrease in rate than with ferrous acetate. Zinc salts deactivated the catalyst seriously. The platinum–iron–tin system was found to afford high yields of crotyl alcohol in the hydrogenation of crotonaldehyde over supported platinum catalysts.[53] The selectivity depended greatly on the support. The platinum catalysts supported on carbon and calcium carbonate produced crotyl alcohol preferentially, while butyraldehyde was formed over the catalysts supported on barium sulfate and alumina. Other selective platinum catalyst systems as studied in the hydrogenation of cinnamaldehyde are Pt–Sn–nylon,[54] Pt–Ge–nylon,[55] and the Pt–graphite heated at 500°C under hydrogen and then at 900°C under vacuum.[56]

The hydrogenation of citral [geranial (**1**)–neral mixture] over platinum oxide could be controlled to almost completely stop after absorption of 1 equiv of hydrogen to give geraniol (**2**) (and nerol) or to give citronellol (**3**) with uptake of 2 mol of hydrogen, by adjusting the amounts of the catalyst and/or the additives (eq. 5.24).[51]

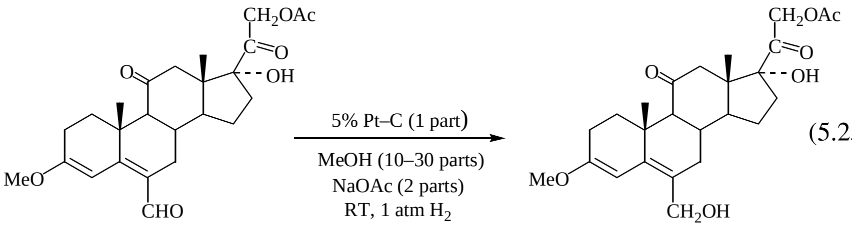


(5.24)

Ferric chloride–doped Ru–C was used for the hydrogenation of **1** in a methanol solution containing a small amount of triethylamine.[57] A 97% yield of a mixture of **2** and nerol was obtained along with a small amount of **3**. Galvagno et al. studied the effects of metal dispersion and the addition of tin in the hydrogenation of cinnamaldehyde and **1** with carbon- and alumina-supported ruthenium catalysts in 95% ethanol at 60°C and atmospheric hydrogen pressure.[58] In the hydrogenation of cinnamaldehyde over Ru–C catalysts, selectivity to cinnamyl alcohol increased with increasing ruthenium loading (the larger ruthenium particles) from ~30% at 0.5 wt% Ru up to >60% at 10 wt% Ru; however, in the hydrogenation of **1**, selectivity to unsaturated alcohols remained constant regardless of the extent of ruthenium loading. Addition of tin to ruthenium decreased the catalytic activity but increased the selectivity to unsaturated alcohols up to 90% with both cinnamaldehyde and **1**.

Didillon et al. studied the hydrogenation of **1** using bimetallic Rh–$SnBu_2$–SiO_2 catalysts obtained by treating Rh–SiO_2 with $SnBu_4$ in heptane at 100°C and 5 MPa H_2 for 1 h. When **1** was hydrogenated over the Rh–Sn catalysts of various Sn/Rh ratios in heptane at 77°C and 7.6 MPa H_2, the selectivity for **3** increased up to a value of 81% at 100% conversion for a Sn/Rh ratio of 0.12. Above these ratios, the selectivity for **3** decreased and the selectivity for **2** and nerol increased up to 96% at 100% conversion for a Sn/Rh ratio of 0.92.[59] Similarly prepared Rh–Ge and Rh–Pb catalysts have also been studied. However, the selectivities for **2** with these catalysts were lower, and thus the sequence in selectivity with respect to the modifying metal was found to be Sn > Ge >> Pb.[60] In the hydrogenation of substituted acroleins over Al_2O_3-supported ruthenium catalysts, Coq et al. obtained the observation that Sn was the only additive that promoted the selectivity for formation of allylic alcohols among the metal ions studied (Sn, Fe, Zn, Ge, Sb).[61]

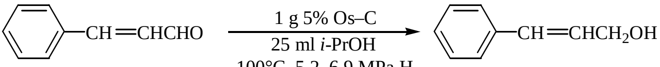
3-Alkoxy-6-formyl-3,5-diene steroids are hydrogenated to the corresponding 6-hydroxymethyl steroids without difficulty employing a Pt–C catalyst in a slightly basic medium.[62] For example, 6-formylcortisone 21-acetate 3-enol ether (**4**) was hydrogenated selectively at the C6 formyl group under the conditions described (eq. 5.25). With use of borohydrides, the 6-formyl and 20-oxo functions were reduced at comparable rates. Thus, by the hydrogenation over Pt–C the 6-hydroxymethyl 3-enol ethers derived from cortisone acetate, deoxycorticosterone acetate, and androst-4-ene-3,17-dione have been prepared in good yields. The hydrogenation over Raney Ni also proved useful. The success in the selective hydrogenation of the 6-formyl group over these catalysts is presumed to be due to an unreactive nature of the 3,5-diene system resulting not only from its high degree of substitution but also from its adsorption to the catalyst made weaker by a strongly electron-releasing 3-alkoxy group in a basic medium.



(5.25)

4 (2 parts)

Osmium and iridium catalysts have been shown to be highly selective for the formation of unsaturated alcohols by hydrogenation of α,β-unsaturated aldehydes without any additive. Good yields of allyl alcohol (73%), crotyl alcohol (90%), and cinnamyl alcohol (95%) (eq. 5.26) were obtained by the hydrogenation of acrolein, crotonaldehyde, and cinnamaldehyde, respectively, over 5% Os–C catalyst both with and without solvent.[63]



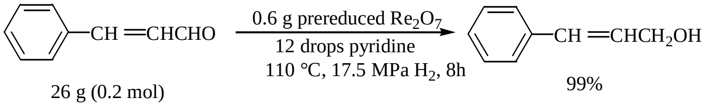
10 g (0.76 mol)

95% (GC)

(5.26)

High yields of allylic alcohols have also been obtained in the hydrogenation of α,β-unsaturated aldehydes over 5% Ir–C catalyst in ethanol at room temperature and atmospheric pressure of hydrogen (Table 5.1).[64] With acrolein, however, the yield of allyl alcohol was lower (60%).

Prereduced rhenium heptoxide catalyst,[65] especially the catalyst poisoned with pyridine, has been found to give high yields of unsaturated alcohols in the hydrogenation of unsaturated aldehydes (Table 5.2).[66] A typical hydrogenation with the rhenium catalyst is shown in eq. 5.27. In the vapor phase hydrogenation of acrolein to allyl alcohol, the selectivity of rhenium catalysts has been found to be improved by poisoning with CO and CS_2.[67]

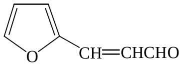
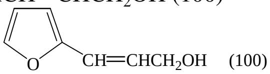
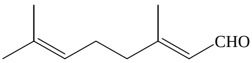
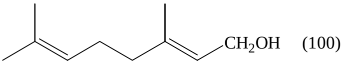


(5.27)

Nagase et al. studied the hydrogenation of crotonaldehyde over a Ag–Mn catalyst supported on $Al_2O_3 \cdot 5AlPO_4$ in hexane at 5 MPa H_2.[68] The high activity and selectivity to crotyl alcohol was obtained over Ag–Mn catalysts with >1.5 Mn/Ag atom ratio at 180°C (72.0% selectivity at 98% conversion, compared to 43.2% selectivity at 84.3% conversion over the catalyst without Mn).

Cobalt catalysts are generally accepted to be more selective than nickel catalysts in the hydrogenation of α,β-unsaturated aldehydes to allylic alcohols.[69] Hotta and Kubomatsu found that 2-methyl-2-pentenal was selectively hydrogenated to 2-

TABLE 5.1 Selective Hydrogenation of α,β-Unsaturated Aldehydes to Allylic Alcohols over Ir–C Catalyst[a,b]

Aldehyde	$T_{1/2}$ (min)	Product (%)
$CH_2{=}CHCHO$	70	$CH_2{=}CHCH_2OH$ (60) $CH_3CH_2CH_2OH$ (12) CH_3CH_2CHO (28)
$CH_3CH{=}CHCHO$	60	$CH_3CH{=}CHCH_2OH$ (96) $CH_3CH_2CH_2CH_2OH$ (4)
$PhCH{=}CHCHO$	60	$PhCH{=}CHCH_2OH$ (100)
	70	
	70	

[a]Data of Bakhanova, E. N. et al. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1972**, *9*, 1993 (*CA* **1973**, *78*, 15967e).
[b]The aldehyde (6.0 mmol) was hydrogenated with 5% Ir–C (0.5 g) in 96% EtOH (10 ml) at room temperature and atmospheric pressure.

TABLE 5.2 Hydrogenation of Unsaturated Aldehydes over Prereduced Rhenium Heptoxide Poisoned with Pyridine[a,b]

Aldehyde	Reaction Temperature (°C)	Conversion (%)	Yield of Unsaturated Alcohol (%)
Crotonaldehyde	90	96	86
α-Methylcrotonaldehyde	115	98	83
Cinnamaldehyde	110	100	99
α-Methylcinnamaldehyde	120	100	99
Citral	100	100	66[c]
Citronellal	140	100	96

[a]Data of Pascoe, W. E.; Stenberg, J. F. in *Catalysis in Organic Syntheses*; Jones, W. H., Ed.; Academic Press: New York; 1980, p 11. Reprinted with permission from Academic Press Inc.
[b]For a typical hydrogenation, see eq. 5.27.
[c]Yield of geraniol and nerol.

methyl-2-penten-1-ol over Raney Co in the presence of metal salts such as iron, cobalt, manganese, and nickel chlorides.[70,71] Over Raney Co modified with ferrous chloride, hydrogenation of the pentenal gave the unsaturated alcohol in more than 80% selectivity in 2-propanol at 55°C and atmospheric hydrogen pressure. It was found that the color of the reaction mixture changed to blue, indicating the presence of Co^{2+} ion. Increasing amounts of added $FeCl_2$ decreased markedly the rate of hydrogenation of the C=C double bond while the rate of hydrogenation of the aldehyde group decreased only slightly. The addition of such modifiers as $FeCl_2$, $CdCl_2$, or $CoCl_2$ to Raney Ni was not effective in producing unsaturated alcohols in the hydrogenation of 2-methyl-2-pentenal and cinnamaldehyde.[72] Nitta et al. found that, while the catalysts prepared from cobalt chloride as the starting material were highly active and selective in the hydrogenation of crotonaldehyde and cinnamaldehyde, this was not the case for the hydrogenation of acrolein. The catalysts prepared from cobalt nitrate showed high activities, and the selectivities depended largely on the support and solvent employed. The selectivity also increased with increasing size of cobalt crystallites. A relatively high selectivity to allyl alcohol up to 33% at 50% conversion was obtained in 2-propanol with a Co–SiO_2–Al_2O_3 reduced at 500°C for 1 h.

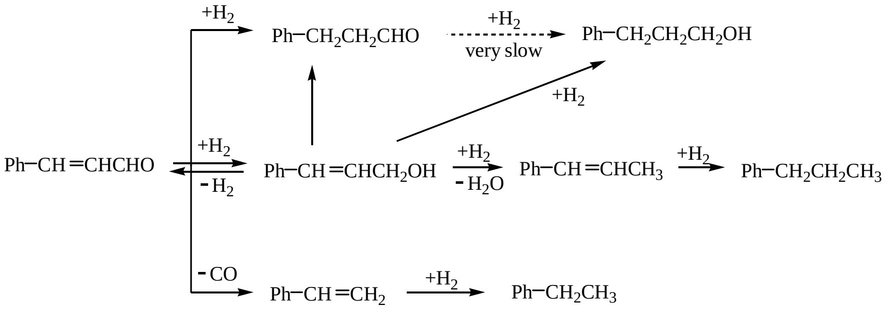
Vapor-phase hydrogenation of crotonaldehyde has also been studied mostly over platinum-based catalysts. Improved selectivity for the carbonyl hydrogenation has been obtained with platinum catalysts modified by Sn, Fe, Ni, and Ga and by the partially reducible support TiO_2.[73,74] According to Raab et al., the catalytic activity for hydrogenation of the C=O group decreased in the order Pt–Ga–SiO_2 > Pt–TiO_2 > Pt–Sn–TiO_2 > Pt–Ni–SnO_2 as compared at a coversion of crotonaldehyde below 10% between 80 and 140°C at partial pressures of 0.006 and 0.0953 MPa of the aldehyde and hydrogen, respectively. The highest selectivity to crotyl alcohol was 56% for Pt–Ga–SiO_2, 46% for Pt–TiO_2 and 31% for Pt–Sn–SiO_2. Pt–SiO_2 was one order of magni-

tude less active than the other catalysts and catalyzed only the hydrogenation of the C=C bond. Coloma et al. have discussed the effects of tin in bimetallic Pt–Sn supported on pregraphitized carbon black in vapor-phase hydrogenation of crotonaldehyde.[75] A relatively important amount of Sn^{2+} was reduced to Sn^0 to form Pt–Sn alloys. The oxidized species of tin had a promoting effect of the hydrogenation of the C=O group. A Pt–Sn alloy formation greatly improved the catalytic activity in spite of the fact that the amount of platinum was reduced. The dilution of surface platinum by metallic tin would hinder the hydrogenation of the C=C bond. Thus, the presence of tin had a very important effect for increasing the selectivity for the formation of crotyl alcohol.

Reduced Ni–Cu[76,77] and Raney-type Zn,[78] Cu–Zn,[79] Cu–Cd,[80] and Ag–Zn[81] catalysts have been reported to be selective in the hydrogenation of acrolein or crotonaldehyde in vapor-phase or liquid-phase hydrogenation. In the hydrogenation of acrolein in ethanol at 120°C and an initial H_2 pressure of 5 MPa, Raney Ag–Zn (1:1) catalyst was superior to Raney Cu, Zn, or Ag catalysts in the selectivity to allyl alcohol; an 86.6% selectivity was obtained at 69.8% conversion. The selectivity to allyl alcohol further increased to 95% by the addition of a small amount of Fe^{3+} ion with a slight decrease in conversion.[81] An effective catalyst for the selective hydrogenation of acrolein to allyl alcohol described by Ueno et al. consisted of 10% Ag, 25% Cd, 73.9% ZnO, and 13.6% SiO_2, and was prepared by adding 4.4 g $Si(OMe)_4$ to a solution of 2 g $AgNO_3$, 0.917 g $Cd(NO_3)_2$, and 34.7 g $Zn(NO_3)_2$ in 30 ml MeOH and 13 ml H_2O, stirring at 90°C for 30 min, drying, and calcining at 350°C for 5 h followed by reduction with hydrogen.[82] Hydrogenation of acrolein with this catalyst at 200°C and 1.47 MPa H_2 gave allyl alcohol with 54% selectivity at 90% conversion.

In vapor-phase hydrogenation of crotonaldehyde over Rh–Sn–SiO_2 catalysts, the selectivity to *trans*- and *cis*-crotyl alcohol increased strongly with the tin content, reaching 62–69% for the *trans* compound with the Sn/(Sn+Rh) atomic ratio higher than 40%.[83]

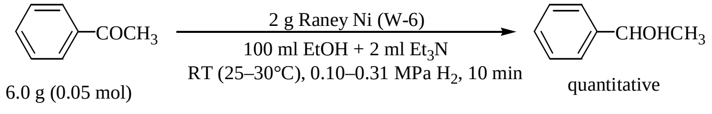
Hydrogenation of α,β-unsaturated aldehydes with palladium catalysts usually afford saturated aldehydes preferentially. However, cinnamaldehyde, the vinylog of benzaldehyde, may be hydrogenated at the aldehyde function to give 3-phenyl-1-propanol and propylbenzene,[84] although usually the hydrogenation to hydrocinnamaldehyde (3-phenylpropionaldehyde) predominates.[36,85,86] The product composition greatly depends on the solvent, the support, and additives.[15,87] Thus hydrogenation of cinnamaldehyde over Pd–C with ferrous chloride in acetic acid or with Pd–kieselguhr in methanol containing hydrochloric acid gives 3-phenyl-1-propanol almost exclusively while hydrogenation with Pd–C–$FeCl_2$ in methanol, Pd–Al_2O_3 in ethanol or Pd–kieselguhr in acetic acid gives hydrocinnamaldehyde almost quantitatively.[87] The hydrogenation of cinnamaldehyde over palladium catalysts is further complicated by accompanying decarbonylation to give styrene and ethylbenzene as well as by the isomerization or the dehydrogenation followed by hydrogenation of cinnamyl alcohol to give cinnamaldehyde (see Scheme 5.3).[15,88] Formation of higher-boiling products was also recognized.[86] These reactions may also occur over catalysts other than palladium.



Scheme 5.3 Hydrogenation pathways of cinnamaldehyde over palladium catalysts.

5.3 KETONES

Aliphatic and alicyclic ketones are usually hydrogenated without difficulty to the corresponding alcohols over most of the transition metal catalysts under relatively mild conditions unless the ketones are highly hindered. The rate of hydrogenation of the ketones, however, greatly depends on the catalyst, the nature of the solvent, and alkaline or acidic additives, as well as other reaction conditions. Palladium catalysts are seldom active for the hydrogenation of aliphatic and alicyclic ketones except for some steroidal ketones.[89] On the other hand, palladium is an excellent catalyst for the hydrogenation of aromatic ketones, although aromatic ketones may be susceptible to hydrogenolysis to give the corresponding methylene compounds, and to obtain the corresponding alcohols selectively, the catalyst and the reaction conditions must be carefully selected. Raney nickel, especially freshly prepared and highly active catalysts such as W-6,[2] W-7,[90] and T-4,[91] is effective for the hydrogenation of ketones at a low temperature and pressure. Usually the rates of hydrogenation over Raney Ni are greater in alcoholic solvents than in aprotic solvents such as cyclohexane and tetrahydrofuran.[92] The hydrogenation of carbonyl compounds over Raney Ni is often promoted by the presence of a small amount of triethylamine[2] or alkali.[93] Thus the times required for the hydrogenation of various ketones to the corresponding alcohols with W-6 Raney Ni were cut in approximately half with addition of triethylamine. Acetophenone was hydrogenated to 1-phenylethanol in 10 min with addition of triethylamine (eq. 5.28) while 22 min was required in the absence of the base.[2] Insufficiently washed Raney nickel catalysts such as W-7 and T-4 are quite suitable for the hydrogenation of ketones since the alkali remaining in the catalyst may promote the hydrogenation. Blance and Gibson found that lithium hydroxide is a better promoter than sodium hydroxide, and potassium hydroxide is in turn less efficient than sodium hydroxide for promoting the hydrogenation of ketones.[94]



(5.28)

5.3.1 Aliphatic and Alicyclic Ketones

The hydrogenation of ketones over Raney Ni proceeds not always so rapidly under mild conditions and usually requires a considerable time and/or amount of catalyst because of decreasing rate with conversion (see Table 5.3). The activity of Raney nickel is often markedly enhanced by the addition of small amounts of chloroplatinic acid and sodium hydroxide[93] or triethylamine and chloroplatinic acid.[3,4] Delépine and Horeau promoted Raney Ni by treatment with chloroplatinic acid solution, followed by the addition of sodium hydroxide solution.[93] Levering and Lieber added to Raney Ni triethylamine followed by chloroplatinic acid.[3] Blance and Gibson compared both the techniques in the hydrogenation of a variety of ketones over W-4 Raney Ni and found that a combination of the two techniques, specifically, platinizing Raney Ni by adding triethylamine and chloroplatinic acid, followed by addition of sodium hydroxide, is superior to either technique as seen from the results shown in Table 5.3.[94] The best results were obtained with a catalyst promoted by adding triethylamine (3.3 mmol), chloroplatinic acid (0.04 mmol), and finally 10*M* sodium hydroxide (1.2

TABLE 5.3 Time (min) for the Hydrogenation of Ketones over Raney Nickel Catalyst: Effects of Promoters[a,b]

	Promoter					
Ketone	None	NaOH	Et_3N	Pt+NaOH	Et_3N+Pt	Et_3N+Pt+NaOH
2-Propanone	39	24	31	21	25	16
2-Butanone	52	38	47	27	47	19
2-Pentanone	76	36	64	30	83	21
2-Heptanone	77	57	83	33	93	25
4-Methyl-2-pentanone	78	53	—	35	126	27
3-Pentanone	80	—	—	37	221	27
3-Heptanone	82	—	—	38	265	34
2,4-Dimethyl-3-pentanone	*i*	—	—	253	*x*	*i*
Cyclohexanone	40	40	—	21	37	17
4-Methylcyclohexanone	60	45	—	23	36	20
2-Methylcyclohexanone	88	65	—	45	161	32
2,2-Dimethylcyclohexanone	93	70	—	49	167	32
2,2,6-Trimethylcyclohexanone	472	—	—	264	*i*	200
2,2,6,6-Tetramethylcyclohexanone	*i*	—	—	1600	—	1600
Camphor	580	—	—	329	—	153
Acetophenone	57	30	38	19	15	14
Propiophenone	90	55	65	34	24	24
Benzophenone	70	40	39	38	34	16

[a]Data of Blance, R. B.; Gibson, D. T. *J. Chem. Soc.* **1954**, 2487. Reprinted with permission from Royal Society of Chemistry.
[b]The ketone (10 mmol) was hydrogenated with the promoted catalyst (0.5 g) in 20 ml ethanol in the presence of 1–2 mmol NaOH (added as 10*M* solution) at room temperature and 1 atm H_2 (*i* = incomplete reaction; *x* = no absorption of hydrogen).

mmol) to a rapidly stirred suspension of Raney nickel catalyst (0.5 g). The catalyst was then washed 3 times with distilled water and 3 times with ethanol.

Nishimura prepared a platinized T-4 Raney nickel by platinizing and simultaneously leaching Raney alloy; specifically, chloroplatinic acid solution, made alkaline with a small amount of sodium hydroxide, was added to a suspension of Raney alloy in water.[91] The partly leached and platinized Raney alloy was then developed in water, forming a large quantity of bayerite. Partial loss in activity of Raney nickel, which may result on treatment with chloroplatinic acid, could be avoided in this way, and the platinized Raney nickel thus obtained showed a better activity than that platinized by the method of Delépine and Horeau in hydrogenation of typical organic compounds including ketones such as cyclohexanone and acetophenone.

For hydrogenation of larger amounts of ketones and/or in hydrogenation with Ni–kieselguhr or copper–chromium oxide, use of higher temperatures and pressures is preferable as shown in eqs. 5.29[96] and 5.30.[7]

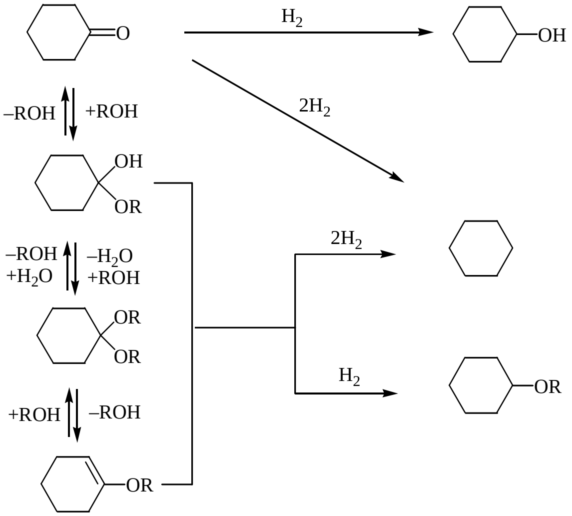
$$\underset{40\text{ g }(0.40\text{ mol})}{(CH_3)_3CCOCH_3} \xrightarrow[100°\text{C, 12.7–1.3 MPa } H_2\text{, 8 h}]{2\text{ g Ni–kieselguhr}} \underset{85\%\text{ (corrected yield, 100\%)}}{(CH_3)_3CCHOHCH_3} \qquad (5.29)$$

$$\underset{205\text{ g }(2.05\text{ mol})}{(CH_3)_3CCOCH_3} \xrightarrow[150°\text{C, 10–15 MPa } H_2\text{, 1.3 h}]{5\text{ g Cu–Cr oxide}} \underset{100\%}{(CH_3)_3CCHOHCH_3} \qquad (5.30)$$

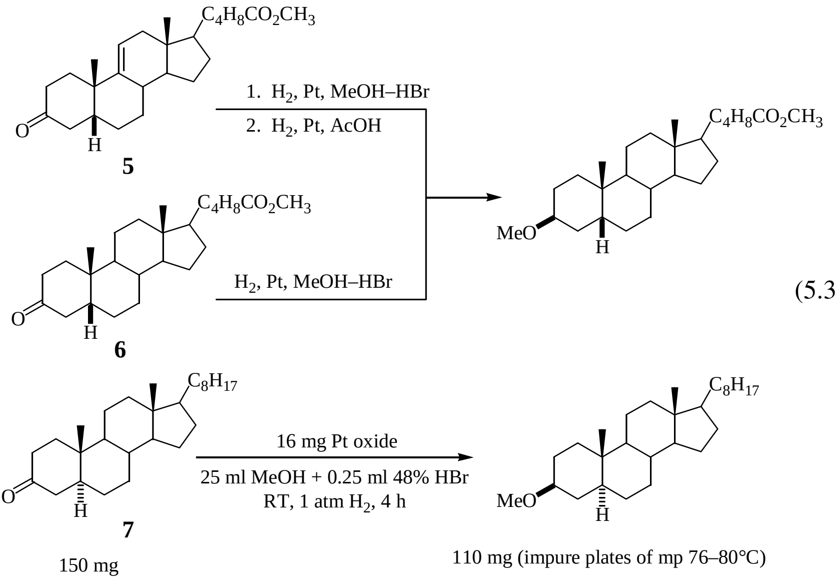
The rates, the products, and the stereochemistry of the hydrogenation of ketones over platinum metals may depend greatly on catalyst, solvent, and acidic or alkaline additive, impurities, as well as the structure of ketones. Breitner et al.[97] studied the rates of hydrogenation of isobutyl methyl ketone, cyclohexanone, and cyclopentanone over 5% Pd–C, Pt–C, Rh–C, and Ru–C catalysts in various solvents (AcOH, H_2O, 0.5*M* aqueous NaOH, 0.5*M* aqueous HCl, MeOH, and EtOAc). Palladium was always not active irrespective of the solvents used. Over Pt–C all three ketones were hydrogenated most rapidly in H_2O and 0.5*M* aqueous HCl, while in 0.5*M* aqueous NaOH only cyclohexanone was hydrogenated in a satisfactory rate. With Rh–C and Ru–C all the ketones were hydrogenated best in H_2O and 0.5*M* aqueous NaOH, and the presence of HCl depressed the rates of hydrogenation, especially for Ru–C.

Hydrogenation of ketones over platinum metals in alcoholic solvents, especially in methanol and ethanol, may be accompanied by the formation of acetals (and also hemiacetals and enol ethers) in the presence of a mineral acid and may lead to the formation of ethers, together with the formation of alcohols and hydrocarbons.[98–100] The reactions involved under these conditions are shown in Scheme 5.4 for cyclohexanone. At an equilibrium in acidic methanol, acetals are present predominantly over hemiacetals for most ketones.[101]

Babcock and Fieser obtained 3β-methoxy steroids by hydrogenation of methyl 3-oxo-$\Delta^{9(11)}$-cholenate (**5**), methyl dehydrolithocholate (**6**), and 5α-cholestan-3-one (**7**) over Adams platinum oxide in methanol in the presence of hydrobromic acid (eq. 5.31).[98] It is noted that the β-methoxy isomers were produced from the ketones of both 5β (**5** and **6**) and 5α series (**7**).



Scheme 5.4 Reactions of cyclohexanone in alcohol in the presence of platinum metals and hydrogen.



(5.31)

Verzele and Acke et al. obtained reasonable to excellent yields of ethers in the hydrogenation of ketones in alcohols with platinum oxide catalyst in the presence of hydrochloric acid (Table 5.4).[99,100]

The acetal formation may occur even in the absence of acid over the platinum metals free from alkaline impurities, particularly over palladium, platinum, and rho-

TABLE 5.4. Percent Yields of Ethers Obtained in the Hydrogenation of Ketones over Adams Platinum Oxide in HCl–Alcohols[a,b]

	Alcohol				
Ketone	MeOH	EtOH	PrOH	*i*-PrOH	Cyclohexanol
2-Propanone	—	—	—	57	—
2-Butanone	95.5	60.5	—	—	—
3-Pentanone	70	52.5	—	—	—
3-Methyl-2-butanone	93	75	92	58	—
4-Heptanone	80	53	67.5	—	—
2,4-Dimethyl-3-pentanone	70	—	—	—	—
5-Nonanone	54	52	—	—	—
2,6-Dimethyl-4-heptanone	77	—	—	—	—
Cyclopentanone	84	90	92	80	—
Cyclohexanone	95	66.5	85	52	39
2-Methylcyclohexanone	80	—	—	—	—
Camphor	46	—	—	—	—
Cycloheptanone	48	—	—	—	—

[a]Data of Verzele, M.; Acke, M.; Anteunis, M. *J. Chem. Soc.* **1963**, 5598. Reprinted with permission from Royal Society of Chemistry. Acke, M.; Anteunis, M. *Bull. Soc. Chim. Belg*. **1965**, *74*, 41. Reprinted with permission from Société Royale de Chimie, Belgium.
[b]The ketone was hydrogenated in 15 molar excess of alcohol (2.5*M* HCl) over Adams platinum oxide (5% by weight of the ketone) at room temperature and atmospheric pressure.

dium.[102] The acetal formation in the absence of acid is probably catalyzed by the adsorbed hydrogen that is ionized on the catalyst surface. Just as in the presence of acid, the hydrogenation of ketones in alcohols with these alkali-free platinum metals may also lead to the formation of ethers together with the formation of alcohols and hydrocarbons. The selectivity to these products may differ greatly by the catalyst and by the structure of ketones. In Table 5.5 are compared the activities and selectivities of platinum, palladium, rhodium, and ruthenium blacks in the hydrogenation of 4-methylcyclohexanone in ethanol.[102,103] It is noted that the metal blacks may be partly poisoned when ethanol (or methanol) is added to the blacks even under the atmosphere of argon. If the blacks are pretreated with hydrogen in cyclohexane and then the cyclohexane is replaced with ethanol, the catalytic activities of the blacks become considerably greater.[104] The palladium and platinum blacks thus pretreated in cyclohexane show greater activities for both the hydrogenation and the acetal formation, but the increase in the rate was found to be much greater for the hydrogenation than for the acetal formation, resulting in increased selectivities for the formation of alcohol and hydrocarbon and decreased selectivities for the formation of ether. It is also noted that the *cis/trans* ratios of the alcohol and the ether formed decreases with the pretreated catalysts except with ruthenium. Usually ethers and hydrocarbons are scarcely formed in the hydrogenation over ruthenium, osmium, and iridium even when the formation of acetals has been observed during hydrogenation.

TABLE 5.5. Hydrogenation of 4-Methylcyclohexanone over Platinum Metals in Ethanol[a,b]

Catalyst	Solvent for Pretreatment with H_2	Rate × 10^4 (mol·min^{-1}g metal^{-1})		Hydrogenation Product				
				Selectivity (mol%)			*Cis/Trans* Ratio	
		k_h[c]	k_a[d]	Alcohol[e]	Hydro-carbon[f]	Etherg	Alcohol[e]	Ether[g]
Pd	EtOH	0.7	64	0.6	0	99.4	2.0	13.5
	Cyclohexane	7.7	110	3.1	0	96.9	0.92	4.39
Pt	EtOH	1.4	12.3	65.0	13.6	21.3	1.87	3.71
	Cyclohexane	26.2	17.2	53.4	36.6	9.9	1.63	1.67
Rh	EtOH	9.5	24.6	96.0	0.3	3.7	10.5	7.67
	Cyclohexane	15.7	27.3	94.3	0.7	5.0	7.69	6.47
Ru	EtOH	35.1	17.3	100	0	0	1.75	—
	Cyclohexane	98.1	12.8	100	0	0	1.95	—

[a]Nishimura, S.; Eto, A. Unpublished results; see also Nishimura et al. *J. Chem. Soc., Chem. Commun.* **1967**, 422; *Chem. Lett.* **1985**, 1275.
[b]4-Methylcyclohexanone (0.05 ml, 0.41 mmol) was hydrogenated over metal black as catalyst (5–20 mg) in 2.5 ml of ethanol at 25°C and atmospheric pressure. The catalysts were prepared by hydrogen reduction of the metal hydroxide, prepared by addition of an aqueous lithium hydroxide to the metal chloride solution or suspension in water, followed by repeated washings with water and hydrogen reductions until the washings no longer become acidic or alkaline.
[c]Rate of hydrogenation: average rate from 0 to ~50% hydrogenation.
[d]Rate of acetal formation at an initial stage of hydrogenation.
[e]4-Methylcyclohexanol.
[f]Methylcyclohexane.
[g]1-Ethoxy-4-methylcyclohexane.

5.3.2 Aromatic Ketones

Aromatic ketones of the type ArCOR (R = alkyl or aryl) may be readily subject to hydrogenolysis to give the corresponding hydrocarbons ($ArCH_2R$), since the benzyl-type alcohols formed (ArCHOHR) are also liable to hydrogenolysis as easily. Over nickel (see, e.g., eq. 5.28) and copper–chromium oxide, this type of hydrogenolysis is seldom significant or is negligible unless the reaction conditions are too vigorous. Various aryl ketones were hydrogenated to the corresponding alcohols in high yields over copper–chromium oxide mostly at 100–130°C and 22–24 MPa H_2 (Table 5.6).[42]

Masson et al. studied the influence of the reaction conditions including temperature, hydrogen pressure, and the nature of solvents on the rate and selectivity for the hydrogenation of acetophenone to 1-phenylethanol over Raney Ni.[105] The ring hydrogenation to give cyclohexyl methyl ketone and the hydrogenolysis to give ethylbenzene or ethylcyclohexane were favored more in cyclohexane than in alcohols, resulting in lower yields of 1-phenylethanol in cyclohexane. The initial rate of hydrogenation was much smaller in methanol and ethanol than in isopropyl alcohol. It was found that the addition of water to isopropyl alcohol increased the rate as well as the selectivity to 1-phenylethanol. Thus, it was possible to obtain a 1-phenylethanol yield

TABLE 5.6 Hydrogenation of Aryl Ketones to Alcohols over Copper–Chromium Oxide[a,b]

Aromatic Ketone	Temperature (°C)	Time (h)	Product (wt %) Aromatic Alcohol	Hydrocarbon
Acetophenone	100–120	0.1	63	5
Butyrophenone[c]	120–130	2.0	74	18
4-Methylbutyrophenone[c]	110–125	2.0	89	6
2,4-Dimethylbutyrophenone	110–130	2.2	90	2
2,4-Dimethylcaprophenone[c]	175	2.2	92	5
Acetomesitylene	110–130	1.5	96	—
Propiomesitylene	135	1.5	87	—

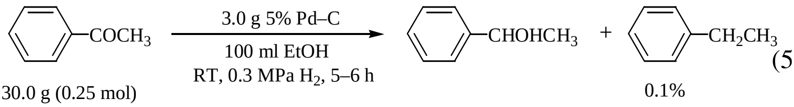
[a]Data of Nightingale, D.; Radford, H. D. *J. Org. Chem.* **1949**, *14*, 1089. Reprinted with permission from American Chemical Society.
[b]The ketone (0.25 mol) in 100 ml methanol was hydrogenated at 22–24 MPa H_2 using 4.0 g of Cu–Cr oxide catalyst.
[c]No solvent.

of 97% with a high reaction rate in isopropyl alcohol containing 30% water at 30°C and 0.9 MPa H_2.

Kumbhar and Rajadhyaksha studied the selective hydrogenation of benzophenone to benzhydrol over Ni and Ni-based bimetallic Ni–Cu and Ni–Fe catalysts in methanol at 135°C and 5.9 MPa H_2.[106] The hydrogenation was accompanied by the formation of an ether, 1-methoxy-1,1-diphenylmethane, in addition to the expected hydrogenation products, benzhydrol and diphenylmethane. With SiO_2-supported catalysts, the selectivity to the ether, which was found to occur by the reaction of benzhydrol with methanol, decreased in the following order: Ni–Cu (75:25)–SiO_2 >> Ni–SiO_2 >> Ni–Fe (75:25)–SiO_2.

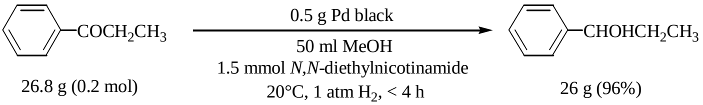
Hydrogenolysis or overreduction of aromatic ketones may occur rather readily over palladium and platinum catalysts, in particular in acidic media. Basic impurities in the catalysts associated with their preparations may have a marked influence on their tendency toward the hydrogenolysis in hydrogenations in a neutral medium.[107,108] For example, acetophenone is hydrogenated to 1-phenylethanol in a neutral solvent over the palladium catalyst prepared by reduction of palladium chloride with formaldehyde and alkali, whereas ethylbenzene is produced even in a neutral solvent over the same catalyst when treated with acid[109] or over the catalyst prepared by reduction of palladium chloride with hydrogen.[110] The behavior of platinum toward the hydrogenolysis also depends on its method of preparation when used in a neutral solvent. Thus 1-phenylethanol was formed quantitatively when acetophenone was hydrogenated over Adams platinum oxide in dioxane, while ethylcyclohexane and/or ethylbenzene was the major product when the reduced platinum oxide that had been washed with dioxane was used in acetic acid or when the catalyst, used in acetic acid and washed with dioxane and water, was employed in dioxane.[107] In contrast to hy-

drogenation for aliphatic ketones, palladium is an excellent catalyst for hydrogenation of aromatic ketones under mild conditions, and may give the corresponding alcohols in high yields when used in neutral medium or in the presence of an appropriate inhibitor. In an example shown in eq. 5.32, 1-phenylethanol containing a trace of starting material and only 0.1% of ethylbenzene was obtained with use of a 5% Pd–C in ethanol at room temperature and 0.3 MPa H_2.[111]



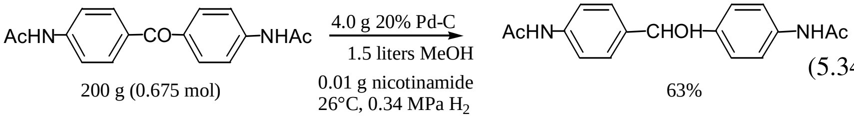
(5.32)

In a patent, a high selectivity to 1-phenylethanol (>99.5% at 90.5% conversion) was obtained by hydrogenation of acetophenone in ethylbenzene (the same amount with acetophenone) over 5% Pd–C at 30°C and 0.62 MPa H_2.[112] Kindler et al. used a small amount of organic base such as morpholine or tetrahydroquinoline to depress the hydrogenolysis of acetophenone to ethylbenzene on palladium catalysts.[39] Since the rate of hydrogenation of acetophenone over Adams palladium oxide in methanol in the presence of tetrahydroquinoline was found to be increased by further addition of *N*,*N*-diethylhexanamide, a small amount of *N*,*N*-diethylnicotinamide was used as an inhibitor in the hydrogenation of propiophenone and thus a high yield of 1-phenyl-1-propanol was obtained within a reasonable time (eq. 5.33).[39]



(5.33)

Werbel et al. applied the Kindler's procedure to the preparation of various 4- or 4,4′-substituted benzhydrols by the hydrogenation of the corresponding benzophenones, using a $Pd(OH)_2$–C catalyst, prepared by the procedure described by Hiskey and Northrop,[113] in the presence of nicotinamide or *N*,*N*-diethylnicotinamide.[114] Thus, the benzhydrols (yields in parentheses) with the substituents, 4,4′-bis(acetylamino) (63%) (eq. 5.34), 4,4′-bis(trifluoroacetamino) (61%), 4-methyl (80%), 4-chloro (35%), and 4-amino (59%), were prepared by hydrogenation of the corresponding benzophenones with the palladium catalyst. In the absence of the inhibitor, 4,4′-bis(acetylamino)benzophenone gave primarily the hydrogenolysis product, 4,4′-bis(acetylamino)diphenylmethane. However, this controlled hydrogenation technique failed for the preparation of benzhydrols with 4-bromo, 4-hydroxy, 4-dimethylamino, 4-acetoxy, 2-carboxy, and 4,4′-bis(dimethylamino) substituents.



(5.34)

In a patent, lead-poisoned palladium catalyst was claimed to be effective for hydrogenation of benzophenone to benzhydrol at 115°C and 0.34 MPa H_2.[115] Kumbhar and Rajadhyaksha hydrogenated benzophenone to benzhydrol in 98.4% selectivity at 88% conversion over Ni–Fe (75:25) on TiO_2 using methanol–10% water as solvent and NaOH (0.1 wt% of benzophenone) as additive at 135°C and 5.9 MPa H_2.[116]

5.3.3 Hydrogenation Accompanied by Hydrogenolysis and Cyclization

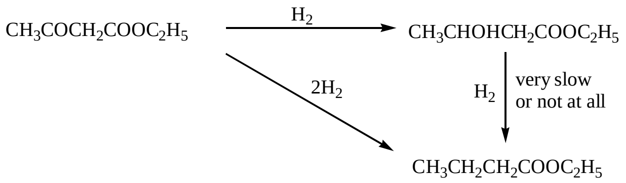
Aliphatic ketones are usually hydrogenated to the corresponding alcohols with little or no hydrogenolysis over most transition metal catalysts except when some unhindered ketones are hydrogenated over platinum catalysts in the vapor phase[117–119] or in acidic media.[120] However, β-keto esters, β-keto amides, and 1,3-diketones may rather readily undergo hydrogenolysis, especially over platinum metals in acidic conditions. Ethyl acetoacetate, a β-keto ester, may be hydrogenated to give ethyl 3-hydroxybutyrate or hydrogenolyzed to give ethyl butyrate. Under mild conditions hydrogenation and hydrogenolysis are competing reactions since ethyl 3-hydroxybutyrate formed is not readily hydrogenolyzed to ethyl butyrate (see Scheme 5.5).

Over Ni–kieselguhr (eq. 5.35, A),[121] copper–chromium oxide (eq. 5.35, B)[7] and Raney Ni (eq. 5.35, C)[122] in ethanol, ethyl acetoacetate is hydrogenated quantitatively to ethyl 3-hydroxybutyrate under the conditions described in eq. 5.35.

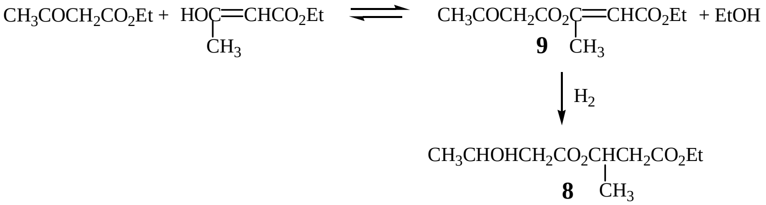
$$CH_3COCH_2CO_2Et \longrightarrow CH_3CHOHCH_2CO_2Et \qquad (5.35)$$

A: Compound 0.39 mol, 2 g Ni–kieselguhr, 50 ml EtOH, 125°C, 8.9 MPa H_2, 2.5 h
B: Compound 0.38 mol, 1 g Cu–Cr oxide, EtOH, 150°C, 10–15 MPa H_2, 3.0 h
C: Compound 0.4 mol, 5 g Raney Ni, EtOH, 23°C, 2 MPa H_2, 16 h

However, over Ni–kieselguhr in the absence of solvent or in ether and methylcyclohexane 32–33% of a diester, ethyl 3-(3′-hydroxybutyryloxy)butyrate (**8**), was produced along with 68–67% of ethyl 3-hydroxybutyrate and small quantities of dehydroacetic acid, and over copper–chromium oxide 16% of the diester and 7% of dehydroacetic acid were formed in the absence of solvent. It was suggested that the diester is formed through the hydrogenation of the intermediate **9**, which results from 2 mol of acetoacetic ester with elimination of 1 mol of ethanol and that the condensation reaction is reversible (Scheme 5.6). Hence, the formation of the diester is depressed in the hydrogenation in ethanol.[121] The reaction pathway in Scheme 5.6 has



Scheme 5.5 Hydrogenation and hydrogenolysis pathways of ethyl acetoacetate under mild conditions.



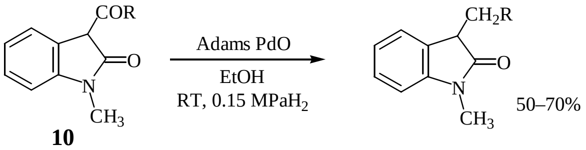
Scheme 5.6 Formation of ethyl 3-(3′-hydroxybutyryloxy)butyrate in the hydrogenation of ethyl acetoacetate.

been supported by the fact that ethyl 2,2-dimethylacetoacetate and ethyl 2-ethyl-2-methylacetoacetate, which are both incapable of enolization, were hydrogenated quantitatively to the corresponding hydroxy esters without a solvent.

Faillebin obtained mainly ethyl butyrate in the hydrogenation of ethyl acetoacetate over pure platinum black regardless of whether it was without solvent or in a solution of ether or hexane, while over the catalyst prepared by the formaldehyde reduction of chloroplatinic acid containing ferric chloride or aluminum chloride, only ethyl 3-hydroxybutyrate was obtained.[123] Ethyl acetoacetate was hydrogenolyzed to an extent of 56% over Adams platinum oxide in acetic acid at room temperature (24–26°C) and atmospheric pressure, while over 3:1 rhodium–platinum oxide under the same conditions the hydrogenolysis was decreased to 11%.[120] Rylander and Starrick examined the hydrogenation of ethyl acetoacetate over platinum metal catalysts in details at room temperature and atmospheric pressure.[124] Over a commercial platinum black in water 90% of ethyl butyrate and 10% of ethyl 3-hydroxybutyrate were formed, but, by the addition of one atom of iron as ferric chloride per atom of platinum, only ethyl 3-hydroxybutyrate was produced. The hydrogenation over Adams platinum oxide or over 5% Pt–C and zinc acetate also afforded ethyl 3-hydroxybutyrate quantitatively. No hydrogenolysis over Adams platinum may be attributed to the presence of alkaline impurities contaminated in it, which functioned to depress the hydrogenolysis completely. In the hydrogenation over various 5% platinum metals-on-carbon catalysts under the same conditions, the extent of hydrogenolysis (figures in parentheses) decreased in the order Pt–C (12%) > Rh–C (10%) > Ir–C (2%) > Ru–C (0%). The amount of hydrogenolysis over Pt–C decreased from 12 to 0 and 1%, respectively, by an increase of temperature (from 26 to 56°C) or hydrogen pressure (from 0.1 to 6.7 MPa). Lease and McElvain hydrogenated a series of ω-acetyl esters of the type $CH_3CO(CH_2)_nCO_2Et$ ($n = 1–5$) to the corresponding hydroxy esters in 82–88% yields over Adams platinum oxide in ethanol (eq. 5.36).[125] The rates of hydrogenation of these keto esters were smaller than that of acetone and, in general, decreased with increasing value of n, although the hydrogenations were completed without any additives.

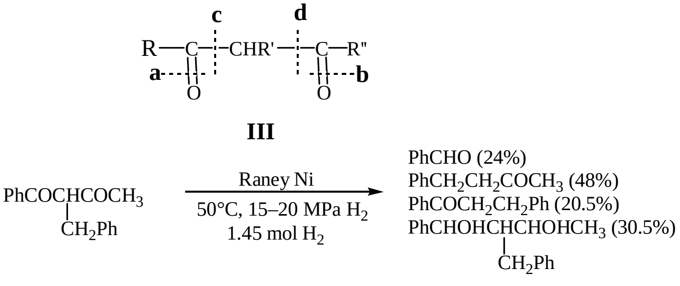
$$\underset{(0.3\ \text{mol})}{CH_3CO(CH_2)_nCO_2Et\ (n = 1\text{–}5)} \xrightarrow[\substack{35\ \text{ml EtOH} \\ \text{RT, 0.2–0.3 MPa } H_2 \\ \text{6–11 h (except for the ester with } n = 4)}]{0.3\ \text{g Adams Pt oxide}} \underset{82\text{–}88\%}{CH_3CHOH(CH_2)_nCO_2Et} \tag{5.36}$$

Similar to β-keto esters, β-keto amides may be readily hydrogenolyzed by conditions. Thus, 3-acyloxyindole (**10**), a β-keto amide, is cleanly hydrogenolyzed to the corresponding 3-alkyl derivative in ethanol over Adams palladium oxide catalyst (eq. 5.37).[126]



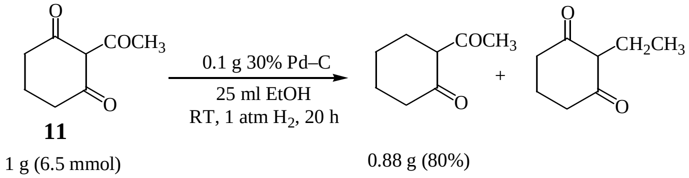
(5.37)

1,3-Diketones are susceptible to hydrogenolysis at either a carbon–oxygen or a carbon–carbon linkage. When the diketone is unsymmetric as indicated by the formula **III** (eq. 5.38), all four linkages indicated by **a**, **b**, **c**, and **d**, may undergo hydrogenolysis to give rather complicated products. Sprague and Adkins hydrogenated various 1,3-diketones (0.15–0.5 mol) in dry ether (30–100 ml) with Raney nickel (4–8 g) at 125°C and 15–20 MPa H_2.[127] The yields of the corresponding 1,3-glycols were 44–99% for most of the unalkylated 1,3-diketones (formula **III**, R′ = H). The cleavage at carbon–carbon linkages **c** and **d** increases with alkylated diketones, especially monosubstituted acetylbenzoylmethanes (formula **III**, R = Ph and R″ = Me). The cleavage may occur even at 50°C, as seen in an example in eq. 5.38, where the cleavage occurred to an extent of 68% and the yield of the corresponding diol was only 30.5%.

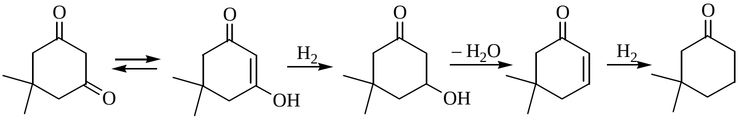


(5.38)

Hydrogenation of 2-acetylcyclohexane-1,3-dione (**11**) over Pd–C in ethanol at room temperature and atmospheric pressure gave the product consisting almost entirely of 2-acetylcyclohexanone, together with a small quantity of 2-ethylcyclohexane-1,3-dione (eq. 5.39).[128] Addition of increasing amounts of sodium hydroxide resulted in an increased yield of 2-ethylcyclohexane-1,3-dione, which reached 45% in the presence of 1 equiv.

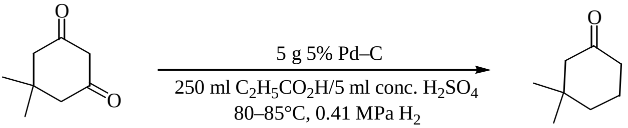


(5.39)



Scheme 5.7 Hydrogenation pathway of 5,5-dimethyl-1,3-cyclohexanedione leading to 3,3-dimethylcyclohexanone.

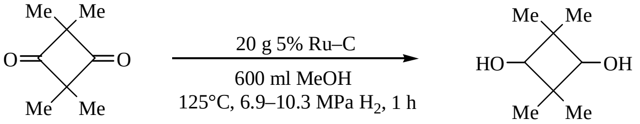
The easy hydrogenolysis of 1,3-cyclohexanedione over palladium catalyst has been applied to the preparation of 3,3-dimethylcyclohexanone from 5,5-dimethyl-1,3-cyclohexanedione (eq. 5.40).[129] The reaction pathway outlined in Scheme 5.7 has been suggested for this transformation. 1,3-Cyclohexanedione was also hydrogenolyzed to give cyclohexanol in a 95% yield over copper–chromium oxide at 200°C and 17.7 MPa H_2.[130]



(5.40)

140 g (1 mol) 69–73%

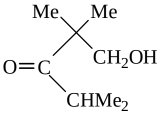
Tetramethyl-1,3-cyclobutanedione, dimethylketene dimer (**12**), was hydrogenated to the corresponding glycol in excellent yields with Ru–C as catalyst in methanol at 125°C and 6.9–10.3 MPa H_2 (eq. 5.41).[131] Hydrogenation over Raney Ni in methanol was often accompanied by formation of a high-boiling byproduct that was shown to consist of 1-hydroxy-2,2,4-trimethyl-3-pentanone (**13**) and methyl 2,2,4-trimethyl-3-oxovalerate (**14**).



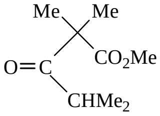
(5.41)

12
400 g (2.86 mol)

403 g (*cis* and *trans*) (98%)



13



14

Török et al. observed that **12** is selectively hydrogenated to the corresponding hydroxy ketone over amorphous Ni–P and Ni–B catalysts in ethanol at 120°C and 7 MPa H_2, while over Raney Ni the corresponding diol was obtained and over Ni–P foil, treated with sulfuric acid during its preparation, the ring-opened product **14** (ethyl ester) was

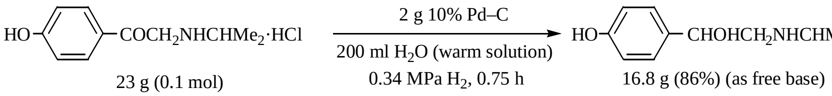
formed exclusively. The formation of **14** was attributed to the acidic centers of the acid-treated Ni–P foil.[132]

Hydrogenation of 1,4- and 1,5-diketones over platinum metals may be accompanied by cyclization to give tetrahydrofurans and terahydropyrans, respectively.[133,134] The hydrogenation of 2,6-heptanedione over Pt–C at 200°C in cyclohexane gave 40% of 2,6-dimethyltetrahydropyran, together with 43% of 3-methylcyclohexanone and 15% of 3-methylcyclohexanol, which resulted by an intramolecular aldol condensation and subsequent hydrogenation.[134]

5.3.4 Amino Ketones

Catalytic hydrogenation of amino ketones to amino alcohols has been a subject of a number of synthetic studies mostly from the viewpoint of pharmacologic interest. The hydrogenation of amino ketones often encounters some difficulty such as a low rate of hydrogenation and the loss of amino groups.

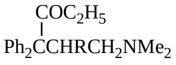
Aromatic amino ketones such as α-aminopropiophenones and ω-aminoacetophenones were successfully hydrogenated as their hydrochlorides in aqueous solutions over Pd–C to give high yields of the corresponding amino alcohols.[135–139] Use of an excess of strong acid should be avoided because of the possibility of hydrogenolysis of the benzyl-type alcohols formed.[135] Corrigan et al. obtained a number of 1-(*p*-hydroxyphenyl)-1-(2-amino)ethanols in 68–91% yields (as free bases) by the catalytic hydrogenation of the corresponding ω-amino-*p*-hydroxyacetophenone hydrochlorides with Pd–C as the catalyst in warm aqueous solution.[136] A typical example is shown in eq. 5.42.



(5.42)

Amidone (6-dimethylamino-4,4-diphenyl-3-heptanone), while resistant to hydrogenation with Raney nickel, could be hydrogenated to the alcohol with platinum oxide as catalyst.[140] However, isoamidone (6-dimethylamino-4,4-diphenyl-5-methyl-3-hexanone)(**15**, R = Me) did not absorb hydrogen in the presence of platinum oxide and the reduction to the corresponding alcohol was achieved by reduction with lithium aluminum hydride.[141]

Hydrogenation of the Mannich-type amino ketones may be accompanied by extensive deamination. Hydrogenation of 4-methoxy-1-(ω-dialkylamino)propionaphthone (**16**) hydrochlorides was successful only over Adams platinum oxide and gave rise to fair yields [52% (crude) or 46% (pure) for R = Bu and 69% (crude) or 53% (pure) for R = Pe] of the amino alcohols, together with some of the hydrogenolysis product, 4-methoxy-1-propionaphthone (22% in the case of R = Bu).[142] With the free bases the products isolated were only dialkylamine and 4-methoxy-1-propionaphthone. With Raney Ni at 0.3–0.4 MPa H_2 only hydrogenolysis took place with the hydrochloride as well as with the free base. With Pd–C at atmospheric pressure the hydrogenation was incomplete even after 6.5 days and only hydrogenolysis products were obtained.



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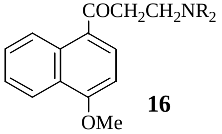

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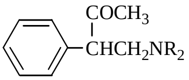
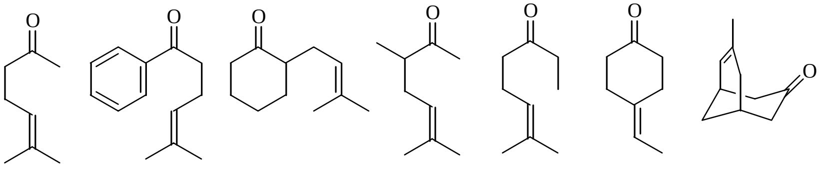


17

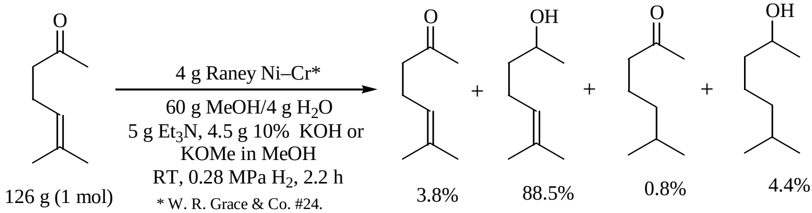
The hydrogenation of 4-chloro-ω-dibutylamino-1-propionaphthone hydrochloride over Adams catalyst was accompanied by a large proportion of cleavage of the nuclear halogen. Hydrogenation of the Mannich-type base derived from phenylacetone, **17**, R = Me, as the hydrochloride in an aqueous solution over Pd–C failed to take place. However, the hydrogenation of the free bases **17**, R = Me and $R_2 = (CH_2)_5$ was successful over Raney Ni in ethanol at 0.34 MPa H_2.[143] Freifelder has reviewed the hydrogenation of various amino ketones.[144]

5.3.5 Unsaturated Ketones

Hydrogenation of unsaturated ketones usually gives saturated ketones and alcohols. However, in the cases where the olefinic bonds are tri- or tetrasubstituted, preferential hydrogenation of the carbonyl group over the olefinic bond may become possible over some catalyst or catalyst system. Gradeff and Formica hydrogenated unsaturated ketones **18a–18e** with trisubstituted carbon–carbon double bonds to the corresponding unsaturated alcohols in good yields using a chromium-promoted Raney Ni in methanol in the presence of a strong inorganic base.[47] The rates were increased by the presence of small amounts of water and an amine. The catalytic system is quite specific. Substitution of the chromium-promoted catalyst by any other metal commonly used in catalytic hydrogenation or omission of the base or methanol resulted in nonselectivity. A typical example is shown in eq. 5.43 for the hydrogenation of **18a**.



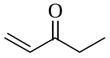
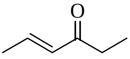
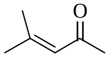
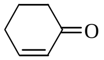
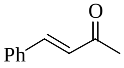
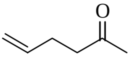
18a **18b** **18c** **18d** **18e** **18f** **18g**



(5.43)

Ishiyama et al. observed that reduced cobalt oxide or Raney Co is the most selective of the transition metals investigated for the preferential hydrogenation of unsaturated ketones to unsaturated alcohols.[145,146] The hydrogenation of unsaturated ketones **18a**, **18f**, and **18g** over cobalt catalyst gave the corresponding unsaturated alcohols in 100%

TABLE 5.7 Hydrogen Transfer Reduction of Unsaturated Ketones over MgO[a,b]

Enone	Conversion (%)	α,β-Unsaturated Alcohol (%)	Non-conjugated Enone (%)	β,γ-Unsaturated Alcohol (%)	Others (%)
	48	43	—	—	5
	89	71	1	4	13
	91	52	1	36	2
	37	15	7	9	6
	77	75	—	—	2
	95	90[c]	1[d]	4[d]	—

[a]Data of Kaspar, J.; Trovarelli, A.; Lenarda, M.; Graziani, M. *Tetrahedron Lett.* **1989**, *30*, 2705. Reprinted with permission from Elsevier Science.
[b]Reaction conditions: MgO (0.005 mol), 250°C, flow of reagents 0.2 ml·min^{-1}, mol (2-propanol)/mol (unsaturated ketone) = 20.
[c]5-Hexen-2-ol.
[d]Mixtures of internal isomers.

selectivity at 50% conversion of substrate in cyclohexane at room temperature and atmospheric pressure. In a competitive hydrogenation of **18a** and 6-methyl-5-hepten-2-ol (the unsaturated alcohol product in eq. 5.43) over Raney Co, the unsaturated alcohol was not hydrogenated until **18a** had been completely converted to the unsaturated alcohol. The selectivity of the metals for formation of unsaturated alcohols decreased in the order Co >> Ni, Os >> Ir, Ru, Rh, Pd, Pt. The selectivity of cobalt and nickel catalysts were increased by treatment with an alkaline solution, while the selectivity was completely lost when the catalysts were poisoned with carbon monoxide.

α,β-Unsaturated ketones may be selectively hydrogenated to allylic alcohols in a flow system with MgO as catalyst and 2-propanol as hydrogen donor.[147] Typical results are shown in Table 5.7. A short contact time [LHSV (liquid hourly space velocity) = 9.0 h^{-1}] in a flow system is essential for minimizing the formation of undesirable byproducts, which is increased by the high basicity of MgO and a long reaction time as it is the case in a batch system. Side reactions may be minimized by doping the MgO catalyst with HCl to decrease its basicity.[148]

5.4 STEREOCHEMISTRY OF THE HYDROGENATION OF KETONES

The stereochemistry of hydrogenation of ketones has been a subject of continuing interest, particularly for alicyclic ketones, and there have been a large body of investigations on their hydrogenations. The results on the hydrogenation of substituted cyclohexanones and of cresols were generalized by von Auwers[149] and Skita,[150,151] and later modified by Barton[152] on the basis of the concept of conformation and the steric effect of substituents. The generalized rule, now referred to as the *von Auwers–Skita–Barton rule* (ASB rule), may be summarized as follows:

1. Catalytic hydrogenation of both hindered and unhindered cyclohexanones in strongly acidic media (rapid hydrogenation) leads to the alcohols rich in the axial isomer.
2. Catalytic hydrogenation in neutral or alkaline media (slow hydrogenation) leads to the alcohols rich in the equatorial isomer if the ketone is not hindered and to those rich in the axial isomer if it is strongly hindered.
3. Catalytic hydrogenation in the vapor phase of isomeric cresols over nickel catalysts at a high temperature leads to alcohols rich in the equatorial isomer.

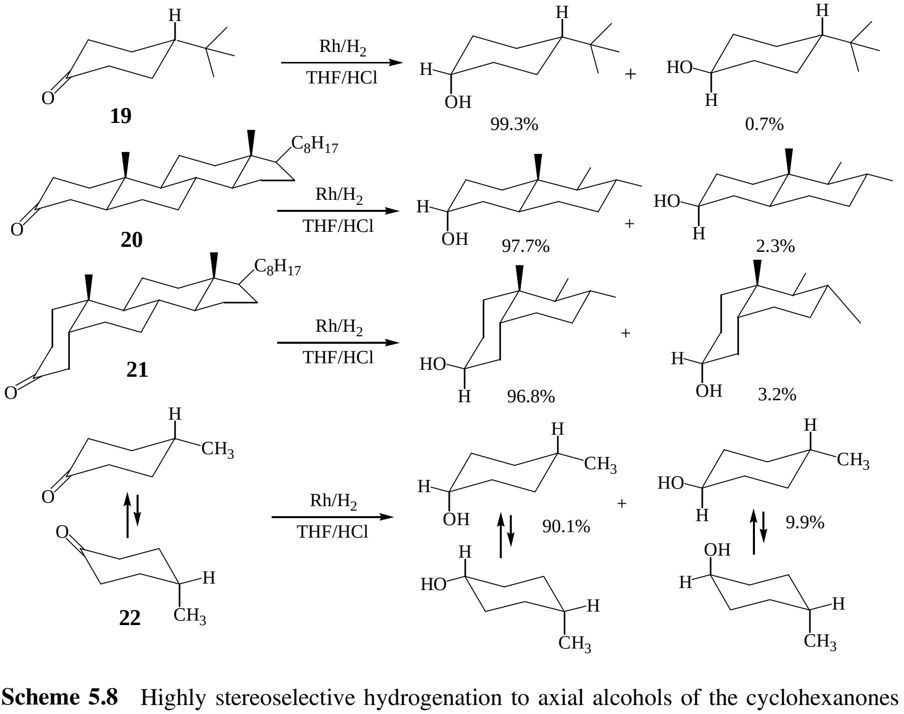
Rules 1 and 2 may be accepted as a generalization based primarily on the results obtained over platinum catalysts. However, there have been known many examples of the exception to this rule,[153] since the stereochemistry of hydrogenation may be influenced by many factors, such as the solvent, the temperature, the hydrogen pressure, and the basic or acidic impurity associated with catalyst preparation, as well as the activity of the catalyst, and since the effects of these factors may differ sensitively with the catalyst employed and by the structure of the ketone hydrogenated.

5.4.1 Hydrogenation of Cyclohexanones to Axial Alcohols

As generalized in the ASB rule 1, many axial alcohols have been obtained by hydrogenating substituted cyclohexanones over platinum catalysts in the presence of hydrochloric acid. However, this method has the following disadvantages:

1. The hydrogenations over platinum may be accompanied by hydrogenolysis to give hydrocarbons, especially with unhindered ketones in acidic media.
2. The stereoselectivities are not always very high, particularly in the cases of unhindered ketones.[154–158] For example, only 78% of the *cis* (axial) isomer was formed in the hydrogenation of 4-*t*-butylcyclohexanone over platinum oxide in AcOH-HCl.[156]
3. When acetic acid, in which better stereoselectivities are usually obtained, is used as the solvent in such strongly acidic condition, acetylated products may be formed and neutralization of the solvent and hydrolysis of the products are often required to isolate the alcohols produced.

Another useful method using a heterogeneous catalyst is the hydrogenation over rhodium catalyst. High stereoselectivities to axial alcohols have been obtained with rhodium catalysts in the hydrogenation of 4-methylcyclohexanone,[102,159] 4-*t*-butylcyclohexanone,[153c] and 5α- and 5β-cholestan-3-ones[153d] in ethanol. The stereoselectivities are further improved in the presence of hydrochloric acid.[159] However, under these conditions significant amounts (4–16%) of the corresponding ethoxy compounds and small amounts of hydrogenolysis products are formed as byproducts.[153c,153d,160] The formation of these byproducts can be depressed almost completely by using isopropyl alcohol or tetrahydrofuran as the solvent without losing the high stereoselectivities.[161] Compared to the hydrogenation in isopropyl alcohol, in tetrahydrofuran the addition of hydrochloric acid in far smaller amounts was sufficient for obtaining high stereoselectivities and excess amounts of hydrochloric acid retarded the hydrogenations seriously. This method using rhodium catalyst, however, fails with hindered cyclohexanones, where the rates of hydrogenation become very small and very high stereoselectivities are not obtained.[159] Examples of the stereoselective hydrogenation of typical unhindered ketones over a rhodium black in the presence of hydrochloric acid are shown in Table 5.8.[161] Scheme 5.8 indicates that the stereoselectivity to axial alcohol is especially high with 4-*t*-butylcyclohexanone (**19**) and 5α- and 5β-cholestan-3-ones (**20** and **21**) with fixed conformations, compared to that with 4-



Scheme 5.8 Highly stereoselective hydrogenation to axial alcohols of the cyclohexanones with a fixed conformation.

TABLE 5.8 Stereoselective Hydrogenation of Unhindered Cyclohexanones to Axial Alcohols over Rhodium Catalyst[a,b]

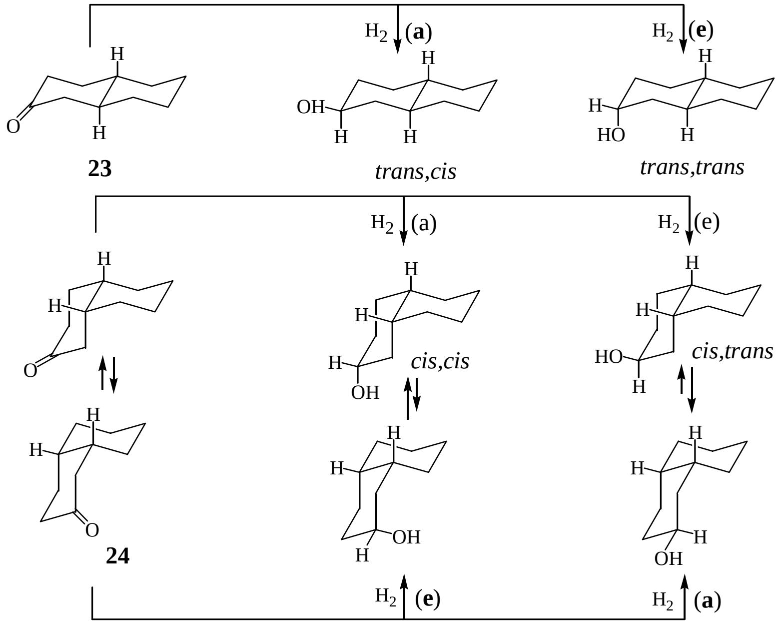
					Product (%)[d]		
Ketone (mg)	Catalyst (mg)	Solvent (ml)	HCl Added (ml)[c]	Time (h)	Axial Alcohols	Equatorial Alcohols	Others
4-Methylcyclohexanone (100)	5	THF, 2	0.001	4	90.1	9.9	0.0
4-*t*-Butylcyclohexanone (100)	5	*i*-PrOH, 2.5	0.02	3	99.2	0.5	0.3
(500)	20	THF, 5	0.006	3	99.3	0.7	0.0
5α-Cholestan-3-one (500)	10	*i*-PrOH, 30	0.16	4.5	95.4	3.8	0.8
(200)	20	THF, 3.5	0.004	3	97.5	2.3	0.2
5β-Cholestan-3-one (500)	10	*i*-PrOH, 12	0.08	4	96.3	2.7	1.0
(200)	20	THF, 3	0.004	3	96.6	3.2	0.2
17β-Hydroxy-5α-androstan-3-one (30)	12	THF, 2	0.002	1.3	92.0	7.9	0.1
5α-Androstane-3,17-dione (200)	10	THF, 2.5	0.002	2	96.6[e]	2.7	0.7[f]
5β-Androstane-3,17-dione (100)	6	*i*-PrOH, 3	0.02	1.7	98.8[g]	0.2	1.0
5α-Pregnane-3,20-dione (100)	10	THF, 2	0.002	2.5	94.8[h]	2.6	2.6[f]

[a]Data of Nishimura, S.; Ishige, M.; Shiota, M. *Chem. Lett.* **1977**, 963. Reprinted with permission from Chemical Society of Japan.
[b]The ketones were hydrogenated at 25°C and atmospheric pressure.
[c]37% hydrochloric acid.
[d]GC analysis.
[e]3α-Hydroxy-5α-androstan-17-one.
[f]Mostly the corresponding diols.
[g]3β-Hydroxy-5β-androstan-17-one.
[h]3α-Hydroxy-5α-pregnan-20-one.

methylcyclohexanone (**22**) with a less fixed conformation. Since the hydrogenation of hindered ketones proceeds only very slowly with rhodium catalyst,[162] use of rhodium catalyst is also advantageous for the selective hydrogenation of a compound with two oxo groups of different steric requirements such as 3,17- and 3,20-dioxo steroids (see Table 5.8).

Hydrogenation of *trans*-2-decalone (**23**) with a fixed conformation gave *trans,trans*-2-decalol (the axial alcohol) in a high stereoselectivity of 98% both with rhodium catalyst in THF–HCl and with platinum catalyst in AcOH–HBr. On the other hand, the hydrogenation stereochemistry of *cis*-2-decalone (**24**) is complicated by the two interconvertible conformations as shown in Scheme 5.9. A mixture of 66% *cis,trans* and 34% *cis,cis* isomers was obtained over rhodium in THF–HCl. Similarly, a mixture of 44% *cis,trans* and 56% *cis,cis* isomers was produced over platinum in AcOH–HBr.[163]

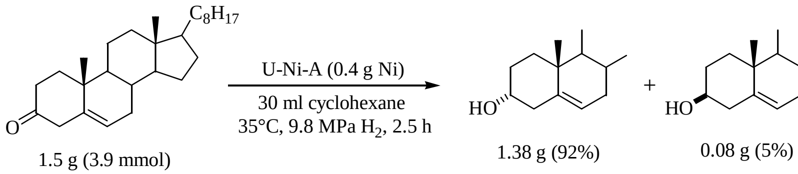
As in an example of *trans*-2-decalone described above, the hydrogenation of substituted cyclohexanones with platinum catalysts usually gives higher yields of axial alcohols in the presence of hydrobromic acid than in the presence of hydrochloric acid. Ruzicka et al. obtained 5α-cholestan-3α-ol in 67% yield by hydrogenating 5α-cholestan-3-one (62 g, 0.16 mol) with platinum oxide (12 g) in Bu_2O (1200 ml)–HBr (48%, 3 ml) at 65–70°C. Similarly, 5β-cholestan-3β-ol was obtained in 95% yield in the hydrogenation of 5β-cholestan-3-one (40 g, 0.10 mol) over platinum oxide (8 g) in AcOH (1200 ml)–HBr (48%, 8 ml) at 60°C.[155] The proportion of hydrogenolysis



Scheme 5.9 Stereochemistry of the hydrogenation of *cis*- and *trans*-2-decalones: (**a**) axial attack of hydrogen; (**e**) equatorial attack of hydrogen.

also decreases in the presence of hydrobromic acid, although the rate of hydrogenation becomes smaller than in the presence of hydrochloric acid. Similarly, 4-*t*-butylcyclohexanone (20 mg, 0.14 mmol) was hydrogenated to give *cis*-4-*t*-butylcyclohexanol in a 98% stereoselectivity in hydrogenation over a platinum black (3 mg) in AcOH (2 ml)–HBr (48%, 17 µmol) at 25°C and atmospheric pressure. The proportion of accompanying hydrogenolysis was reduced from 10.8% in AcOH to 2.5% in AcOH–HBr while the rate of hydrogenation decreased from 14×10^{-4} mol·min^{-1}·g cat^{-1} in AcOH to 8.8×10^{-4} mol·min^{-1}·g cat^{-1} in AcOH–HBr.[164]

Hydrogenation of substituted cyclohexanones over nickel catalysts in the liquid phase usually gives the products rich in axial alcohols, although the stereoselectivities are rarely very high.[153a–153c] High reaction temperature, long reaction time, and the presence of alkali may promote isomerization of the product alcohols, which results in the decrease of the proportions of axial isomers.[153a] The addition of sodium hydroxide, however, was found to increase the formation of axial isomers in the hydrogenation over Raney Ni in ethanol at room temperature and atmospheric pressure.[153c] Thus, the formation of *cis* isomer in the hydrogenation of 4-*t*-butylcyclohexanone over a freshly prepared catalyst increased from 74 to 88% with the addition of sodium hydroxide. The formation of axial isomers also increased when aged Raney nickel was used. For example, hydrogenation of 4-*t*-butylcyclohexanone over the catalyst aged in ethanol for 10 days gave 92% of *cis*-4-*t*-butylcyclohexanol, compared to 74% of the *cis* isomer over the freshly prepared catalyst.[153c] When substituted cyclohexanones are hydrogenated with nickel catalysts under high pressures, axial alcohols are formed predominantly even at elevated temperatures, particularly in methanol or ethanol.[153a,153b,165–167] As an example, the hydrogenation of 3-methylcyclohexanone (150 g) in 250 ml methanol over 3-g Raney Ni at 130°C and 12–9 MPa H_2 afforded 3-methylcyclohexanol consisting of 86% *trans* and 14% *cis* isomers.[167] On the other hand, the hydrogenation of 5α-cholestan-3-one with Urushibara nickel A (U-Ni-A)[168] gave 5α-cholestan-3α-ol, the axial isomer, in an 87% yield (GC) in cyclohexane at 35°C and 9.8 MPa H_2, compared to 51% yield in *t*-butyl alcohol.[169] Thus, a higher stereoselectivity to axial alcohol was obtained in cyclohexane in this case rather than in an alcoholic solvent. This procedure was applied to the stereoselective hydrogenation of 5-cholesten-3-one to 5-cholesten-3α-ol (epicholesterol) in a high yield of 94% (GC) without any isomerization to 4-cholesten-3-one or saturation of the 5,6 double bond (eq. 5.44).[169] No hydrogenolysis occurred as well. The yield was further improved to 99% (GC) by thoroughly removing the water in the catalyst.[170] This method was also applied to the selective hydrogenation of 4-cholestene-3,6-dione and 5α-cholestane-3,6-dione to 3α-hydroxy-5α-cholestan-6-one in 70 and 77% yields, respectively.[171] Similarly, 3α-hydroxy-5α-cholestan-7-one was obtained from 5α-cholestane-3,7-dione in 77% yield.



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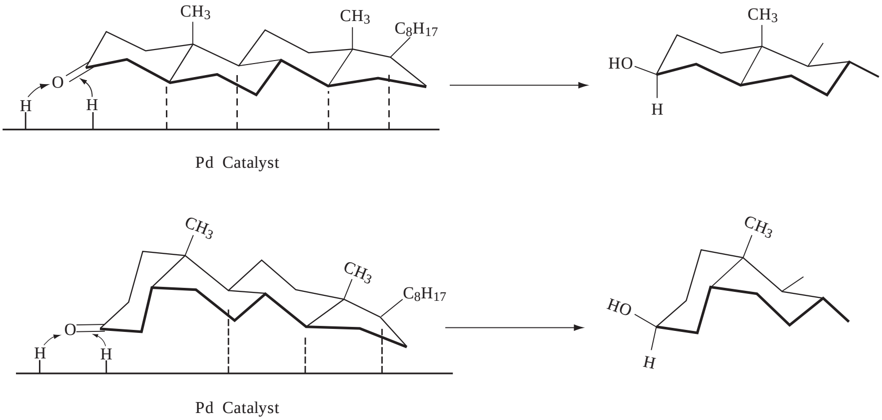
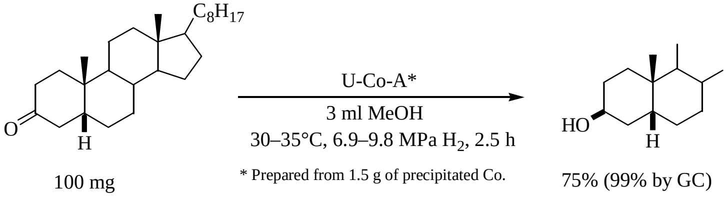


Figure 5.1 Stereochemistry of the hydrogenation of 5α- and 5β-cholestan-3-ones on palladium based on a strong interaction of the steroid α face with the catalyst. (From Nishimura, S.; Murai, M.; Shiota, M. *Chem. Lett.* **1980**, 1239. Reproduced with permission of Chemical Society of Japan).

On the other hand, 5β-cholestan-3-one was hydrogenated to the axial alcohol, 5β-cholestan-3β-ol, in 99% yield (GC) over Urushibara cobalt A (U-Co-A) in methanol as solvent (eq. 5.45) and in 72% yield (GC) over U-Ni-A.[170] In these cases the yields decreased in less polar solvents over both catalysts.



(5.45)

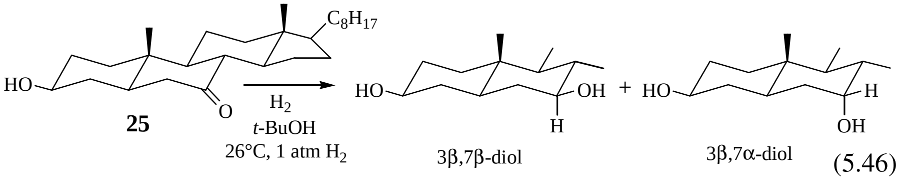
5β-Cholestan-3-one was also stereoselectively hydrogenated to the axial alcohol in 98.5% yield (GC) over a palladium black in isopropyl alcohol at 25°C and atmospheric pressure (see Fig. 5.1 and Section 5.4.2).[153d] Accompanying formation of the isopropyl ether was not observed in the case of the steroid ketone, whereas a large amount (55%) of the ether and an almost 1:1 mixture of *cis* and *trans* alcohols were produced in the hydrogenation of 4-*t*-butylcyclohexanone under the same conditions.

5.4.2 Hydrogenation of Cyclohexanones to Equatorial Alcohols

The stereochemistry of hydrogenation of cyclohexanones in neutral and alkaline media is not as straightforward as generalized in ASB rule 2. If unhindered cyclohexanones are hydrogenated over a platinum catalyst containing no alkaline impurity, the products that are rich in axial alcohols rather than equatorial alcohols are often ob-

tained. For example, the hydrogenation of 4-methylcyclohexanone over Adams platinum oxide in ethanol at room temperature and atmospheric pressure leads to a product rich in equatorial alcohols; however, over the catalyst that was well washed with water or ethanol after reduced to platinum black, a product rich in axial alcohol results under the same conditions.[102,103,172] The stereoisomeric composition of the products may be further complicated by the isomerization of the alcohols produced in hydrogenation at an elevated temperature under a low hydrogen pressure and/or in the presence of alkali.[153a] For example, hydrogenation of 3,3,5-trimethylcyclohexanone (dihydroisophorone) over 2.5% of reduced nickel at 20°C and 6.9 MPa H_2 afforded the product containing 17% of the *cis* (equatorial) isomer while hydrogenation at 130°C gave the product containing 73% of the *cis* isomer. It was observed that 3,3,5-trimethylcyclohexanol containing 90% of the *trans* isomer was isomerized to the alcohol containing 76% of the *cis* isomer over reduced nickel catalyst at 130°C and 6.9 MPa H_2 for 5 h. Since hydrogenation is usually faster than isomerization at low temperatures and/or high pressures, a sufficiently prolonged reaction time will be required to obtain a stereoisomeric equilibrium mixture of the product and; therefore, isomerization of product alcohols does not appear to be important under mild conditions.[173]

In some exceptional cases the product rich in equatorial alcohol may be obtained in a stereoselectivity higher than that expected from the composition at an equilibrium. The hydrogenation of 5α-cholestan-3-one (**20**) over a palladium black in isopropyl alcohol at 25°C and atmospheric pressure afforded a product consisting of 98.9% of equatorial 3β-ol and 1.1% of axial 3α-ol.[153d] This unusually high stereoselectivity, together with the results on 5β-cholestan-3-one (Section 5.4.1), has been explained by a strong interaction of the steroid α face with palladium catalyst, as illustrated in Fig. 5.1. Evidence for supporting this explanation has been obtained from the fact that 5α-cholestan 3-one was reduced 30 times as fast as 4-*t*-butylcyclohexanone in a competitive hydrogenation over palladium in *t*-butyl alcohol at 26°C and atmospheric pressure.[89] Over the other platinum metals, such an unusually high reactivity of the steroid ketone versus 4-*t*-butylcyclohexanone was not observed and the mixture of 3α- and 3β-ols was produced. 3β-Hydroxy-5α-cholestan-7-one (**25**) was similarly hydrogenated stereoselectively to the product containing a 99.4% of equatorial 3β,7β-diol over palladium black under the same conditions (eq. 5.46).[164] A high reactivity of the steroid ketone over 4-*t*-butylcyclohexanone was also observed with **25**, which was hydrogenated 16.6 times as rapidly as 4-*t*-butylcyclohexanone in a competitive hydrogenation. The hydrogenation of **25** over Raney Ni and Raney Co catalysts also gave the equatorial 3β,7β-diol in high stereoselectivities in *t*-butyl alcohol at 26°C



(5.46)

	3β,7β-diol	3β,7α-diol
Pd	99.4	0.6
Raney Ni	95.6	4.4
Raney Co	98.0	2.0

(see eq. 5.46). However, in contrast to palladium, in the hydrogenation of **20** over these base metals the 3-ols mixture containing 28.3 and 32.6% of axial 3α isomer, respectively, were obtained. Also, the unusually high reactivity of the steroid ketone as observed over palladium was not found over these base metal catalysts.[164]

5.4.3 Effects of a Polar Substituent and Heteroatoms in the Ring

The stereochemistry of the hydrogenation of cyclohexanones may be influenced significantly by a polar group substituent or a heteroatom such as oxygen and nitrogen in the ring. For example, hydrogenation of 2- and 4-methoxycyclohexanones over platinum metals gives the alcohols of higher *cis/trans* ratios than in the corresponding methylcyclohexanones, as seen from the results of Table 5.9.[160] It is noted that this trend is particularly pronounced over iridium and platinum catalysts. Senda et al. stud-

TABLE 5.9 *Cis / Trans* Isomer Ratios of the Alcohols formed in Hydrogenation of Methoxy- and Methylcyclohexanones[a,b]

		Cyclohexanone			Cyclohexanone		
Catalyst	Solvent	2-Methoxy	2-Methyl	R_{OMe}/R_{Me}[c]	4-Methoxy	4-Methyl	R_{OMe}/R_{Me}[c]
Ru	EtOH	2.2	1.8	1.2	2.5	2.0	1.3
Rh	EtOH	2.2[d]	2.0[e]	1.1	3.9[f]	3.0[g]	1.3
Pd	EtOH	3.6[h]	1.5[i]	2.4	3.7[j]	1.4[k]	2.6
Os	EtOH	2.8	2.7	1.0	1.9	1.1	1.7
Ir	EtOH	8.2[l]	1.4	5.9	6.3	1.1[m]	5.7
Pt	EtOH	30[n]	3.5[o]	8.6	17p	1.7[q]	10
Pt	*t*-BuOH	67[r]	13[s]	5.2	22[t]	3.5[u]	6.3

[a]Data of Nishimura, S.; Katagiri, M.; Kunikata, Y. *Chem. Lett.* **1975**, 1235. Reprinted with permission from Chemical Society of Japan.
[b]The ketone (0.2 ml) was hydrogenated over 10 mg of catalyst in 5 ml of solvent at 25°C and atmospheric hydrogen pressure. The products other than the corresponding alcohols (A, cyclohexane; B, methylcyclohexane; C, methoxycyclohexane; D, ethoxymethylcyclohexane; E, ethoxymethoxycyclohexane; F, cyclohexanol) are given below in percent.
[c]The ratio of the *cis / trans* isomer ratios of the alcohols from methoxycyclohexanone and from methylcyclohexanone.
[d]Analyzed at 45% hydrogenation. A, 7.3; C, 28.3.
[e]B, 4.3; D, 19.
[f]C, 0.6; E, 3.6.
[g]Analyzed at 67% hydrogenation. B, 1.2; D, 6.1.
[h]Analyzed at 23% hydrogenation. A, trace; C, 15; E, 65.
[i]D, 75.
[j]E, 97.
[k]Analyzed at 86% hydrogenation. D, 98.
[l]Analyzed at 64% hydrogenation.
[m]B, trace; D, 3.5.
[n]Analyzed at 69% hydrogenation. A, 2.0; C and an unidentified product, 2.5; F, 1.3.
[o]B, 0.6; D, 17.
[p]Analyzed at 57% hydrogenation. C, 9.0; E, 10.5.
[q]B, 11; D, 27.
[r]A, 4.9; C, 3.9; F, 4.7.
[s]B, trace.
[t]C, 15.
[u]B, 21.

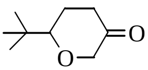
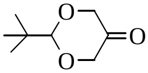
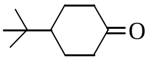
ied the effects of the ring oxygen and nitrogen atoms on the stereochemistry of hydrogenation of cyclohexanone systems.[174,175] A high stereoselectivity to the *cis* alcohol was obtained in the hydrogenation of 6-*t*-butyltetrahydropyran- 3-one (**26**) and 2-*t*-butyl-1,3-dioxan-5-one (**27**), compared with that for 4-*t*-butylcyclohexanone, over all the catalysts investigated (Table 5.10). The results have been explained in terms of an intramolecular n_O–π_{CO} interaction that may favor the adsorption from the equatorial side in **26** and **27**.

The results shown in Table 5.11 show that the addition of hydrogen from the equatorial side is hindered by the presence of the ring oxygen or nitrogen atom. The results have been explained by a similar intramolecular interaction effect of the lone-pair electrons of oxygen or nitrogen atom.

5.4.4 Alkylcyclopentanones

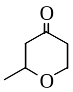
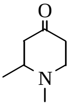
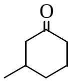
The hydrogenation of 2- and 3-alkyl-substituted cyclopentanones over Raney Ni always affords the *cis* alcohols in greater amounts than the *trans* alcohols.[153b,176,177] In some cases the presence of sodium hydroxide further increases the proportions of the *cis* isomers.[177] The hydrogenation of 2-isopropylcyclopentanone over platinum black (Willstätter) in AcOH–HCl gave the *cis* alcohol in 69% yield[176] and with 2-cyclopentylcyclopentanone the yield of the *cis* isomer decreased to 56%.[153b] On the other hand, the hydrogenation of 2-methylcyclopentanone over Adams platinum catalyst gave the *trans* alcohol predominantly in ethanol[145] as well as in ethanol–hydrochloric acid.[178] 2-Cyclopentylcyclopentanone is hydrogenated to the *cis* alcohol in nearly 90% yield

TABLE 5.10. Percent *Cis* Isomer of the Alcohol Product[a,b]

		Ketone Hydrogenated		
Catalyst	Amount (mg)	 (**26**)	 (**27**)	
Raney Co	1000	80	91	56
Raney Ni	1000	89	97	71
Ru	20	90	91	77
Rh	20	94	100	—[c]
Pd	20	96[d]	100	—[e]
Os	20	66	67	55
Ir	20	70	88	58
Pt	20	81	90	32

[a]Data of Senda, Y.; Terasawa, T.; Ishiyama, J.; Kamiyama, S.; Imaizumi, S. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2948. Reprinted with permission from Chemical Society of Japan.
[b]The ketone (0.5 mmol) was hydrogenated in 3 ml ethanol at room temperature and atmospheric hydrogen pressure. The values were obtained when 50% of the substrate was consumed.
[c]Acetal, 98%.
[d]Acetal, 85%.
[e]Acetal and ethers, 100%.

TABLE 5.11 Percent Alcohols Formed by Addition of Hydrogen from Equatorial Side[a,b]

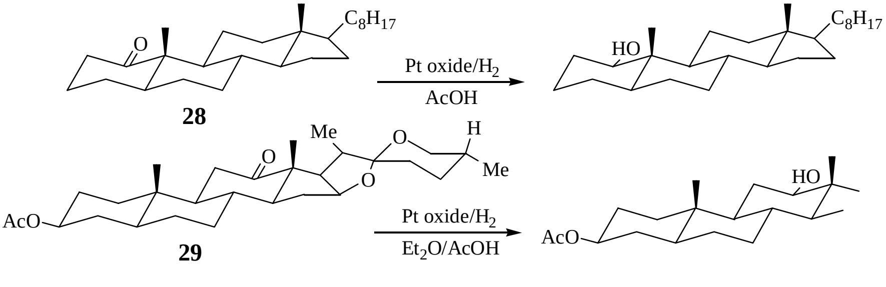
		Ketone Hydrogenated		
Catalyst	Amount (mg)			
Pt oxide	2.5	8	17	77[c]
Pt-C	25	8	15	29
Ru-C	25	38	43	41[c]
Rh-C	25	62	33	88[c]
Pd-C	25	35	11	40[c]
Raney Ni	100	26	31	52[c]
Raney Co	250	26	45	79

[a]Data of Senda, Y.; Okamura, K.; Kuwahara, M.; Ide, M.; Itoh, H.; Ishiyama, J. *J. Chem. Soc., Perkin Trans. 2* **1992**, 799. Reprinted with permission from Royal Society of Chemistry.
[b]The ketone (0.5 mmol) was hydrogenated in ethanol (3 ml) at room temperature and atmospheric hydrogen pressure.
[c]Mitsui, S.; Saito, H.; Yamashita, Y.; Kaminaga, M.; Senda, Y. *Tetrahedron* **1973**, *29*, 1531. Reprinted wth permission from Elsevier Science.

over ruthenium and osmium catalysts in ethanol.[179] The results of the stereochemistry of hydrogenation of alkylcyclopentanones are summarized in Table 5.12.

5.4.5 Hindered Ketones

The addition of hydrogen to hindered ketones usually occurs preferentially from a less hindered side and the stereochemistry is less influenced by the nature of solvents than in the cases of unhindered ketones, as generalized in ASB rules 1 and 2. According to these rules, the axial alcohols are formed predominantly in the hydrogenation of hindered cyclohexanones under both acidic and neutral (or alkaline) conditions. The ABS rule, however, is oversimplified, as pointed out by Dauben et al.,[180] since the addition of hydrogen from a less hindered side does not always give axial alcohols as in the cases of 5α-cholestan-1-one (**28**)[181] and the 12-oxo steroid **29** (hecogenin),[182] where



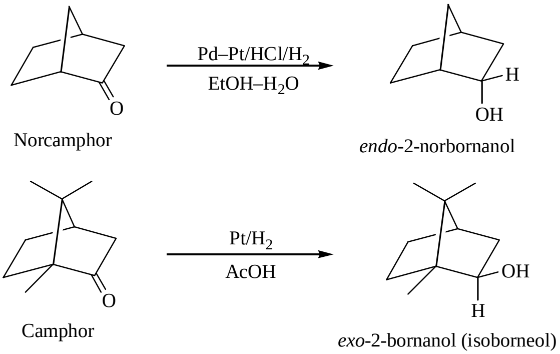
Scheme 5.10 Stereochemistry of the hydrogenation of 1- and 12-oxo steroids.

TABLE 5.12 Stereochemistry of the Hydrogenation of 2- and 3-Alkylcyclopentanones

Cyclopentanone (g)	Catalyst (g)	Solvent (ml)	*T* (°C)	H_2 *P* (MPa)	Time (h)	Cyclopentanol		Ref.
						Cis (%)	*Trans* (%)	
			2-Methyl					
0.1	Pt, 0.005	EtOH, 5	RT	0.1	22[a]	27	73	177
0.1	PtO_2, 0.005	EtOH, 5	RT	0.1	22[b]	26	74	177
0.1	Pd–C, 0.02	EtOH, 5	RT	0.1	32[c]	27	73	177
0.1	Pd–C, 0.02	EtOH, 5	RT	7.8	5[d]	73	27	177
0.1	RaNi, 0.1	EtOH, 5	RT	0.1	20[e]	80	20	177
0.1	RaNi, 0.1	EtOH, 5 + NaOH, 0.008 (g)	RT	0.1	20	81	19	177
			2-Isopropyl					
36	Pt, 2	AcOH, 270 + conc. HCl, 30	RT	0.1	48	64	36	176
148	RaNi, 5	MeOH, 500	80	8	24	69	31	176

				2-Cyclopentyl				
46	Pt, 2.5	AcOH, 405 + conc. HCl, 45	RT	0.1	9	56	44	153b
0.1	Pt, 0.02	EtOH, 5	RT	0.1	5[f]	41	59	177
0.1	PtO_2, 0.02	EtOH, 5	RT	0.1	5[g]	50	50	177
7.7	PtO_2, 0.5	EtOH, 80	RT	0.1	100	51.5	48.5	153b
0.04	Ru, 0.005	EtOH, 1	26	0.1	4	90.4	9.6	179
0.04	Os, 0.005	EtOH, 1	26	0.1	16	89.9	10.1	179
80.5	RaNi, 3	MeOH, 500	180	10–6.5	28.5	72.5	27.5	153b
0.1	RaNi, 0.1	EtOH, 5	RT	0.1	5	73	27	177
				3-Methyl				
0.1	Pt, 0.005	EtOH, 5	RT	0.1	10	75	25	177
0.1	PtO_2, 0.005	EtOH, 5	RT	0.1	10	76	24	177
0.1	RaNi, 0.1	EtOH, 5	RT	0.1	10	66	34	177

[a]92% conversion.
[b]80% conversion.
[c]51% conversion.
[d]37% conversion.
[e]90% conversion.
[f]8% conversion.
[g]9% conversion.



Scheme 5.11 Stereochemistry of the hydrogenation of norcamphor and camphor.

the equatorial 1β- and 12β-ols are formed exclusively as the result of the addition of hydrogen from the less hindered α face (Scheme 5.10). The predominant product in the hydrogenation of bicyclo[2.2.1]heptanones may be an *endo* alcohol or an *exo* alcohol by the steric requirement around the carbonyl group, as shown in Scheme 5.11.[183–185] Hydrogenation of camphor over a reduced iron catalyst, however, was reported to give predominantly *endo*-2-bornanol (borneol).[186]

Wipke and Gund[187] have evaluated the steric congestions of a number of ketones at a reaction center toward nucleophilic addition and correlated them with the stereoselectivity of steric-approach-controlled reactions.[180,188] Since the stereochemistry of hydrogenation of hindered ketones may be controlled by the adsorption of the ketones to the catalyst or the first addition of hydrogen to the carbonyl group, it will be of interest to compare the stereochemical outcome of the hydrogenation of hindered ketones with the stereoselectivity expected by the values of congestions, where "overt" means the least congested side and "covert," the most congested side of ketones. Some of the results in the literature are summarized in Table 5.13.[189–199]

5.4.6 Hydrogenation of Fructose

The hydrogenation of D-fructose leads to a mixture of D-mannitol and D-sorbitol (Scheme 5.12). The diastereoselective hydrogenation of D-fructose to D-mannitol has been a subject of some industrial interest.[200] Usually high selectivities to D-mannitol have been obtained over supported copper catalysts with addition of sodium borate.[201] Hegedüs et al. obtained the highest selectivity of 82.7% of D-mannitol over a cobalt-containing Raney Cu in the presence of sodium borate in the hydrogenation of 20 wt% of D-fructose in water at 50–75°C and 4–7 MPa H_2.[202] An even higher selectivity of 88.2% of D-mannitol was obtained over a CPG (controlled-pore glass)-supported Cu catalyst in the presence of sodium borate.

5.4.7 Enantioselective Hydrogenations

Enantioselective hydrogenation[203] using a heterogeneous catalyst, which was first applied to a carbon–nitrogen double bond,[204,205] has been studied extensively by Izumi

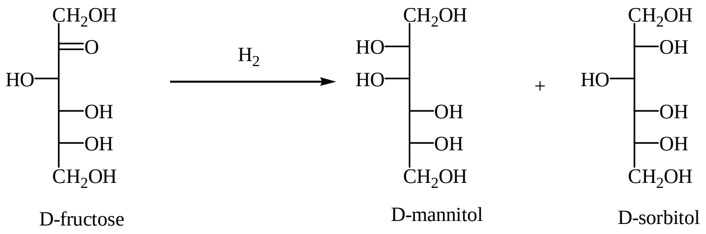
TABLE 5.13 Stereochemistry of Hydrogenation of Hindered Ketones

Ketone	Congestion[a]		Congestion Ratio		Reaction Conditions[b]	Predominant Product (Observed Overt:Covert Ratio)	Ref.
	Overt	Covert	Overt	Covert			
Norcamphor	7.4	30.3	20	80	Pd-Pt/EtOH-H_2O-HCl	*endo*-2-Norbornanol	183
1-Aza-3-norbornanone	—	—	—	—	PtO_2/EtOH[c]	endo-1-Aza-3-norbornanol	189
Camphor	24.4	454.7	5	95	Pt /AcOH	Isoborneol (*exo*:*endo* = >90:5)	185
Fenchone	45.6	99.4	31	69		β-Fenchol	190
Isofenchone	—	—	—	—	PtO_2/AcOH	β-Isofenchol	191
5α-Cholestan-1-one	22.5	69.2	25	75	PtO_2/AcOH	5α-Cholestan-1β-ol	181
5α-Cholestan-2-one	3.2	153.2	2	98	PtO_2/AcOH	5α-Cholestan-2β-ol	192
					U-Ni-A/C_6H_{12} [d]	5α-Cholestan-2β-ol (β:α = 98:2)	170
5α-Cholestan-4-one	3.8	488.3	1	99	PtO_2/AcOH	5α-Cholestan-4β-ol	193
5α-Cholestan-6-one	1.1	386.3	1	99	PtO_2/MeOH	5α-Cholestan-6β-ol	194
5α-Cholestan-7-one	6.4	28.1	18	82	PtO_2/AcOH	5α-Cholestan-7β-ol (α:β = 38:62)	195

TABLE 5.13 Continued

Ketone	Congestion[a]		Congestion Ratio		Reaction Conditions[b]	Predominant Product (Observed Overt:Covert Ratio)	Ref.
	Overt	Covert	Overt	Covert			
5α-Cholestan-11-one[e]	6.6	346.9	2	98	PtO_2/AcOH	5α-Cholestan-11β-ol (exclusive)	196
5α-Cholestan-12-one	24.5	56.8	30	70	PtO_2/AcOH	5α-Cholestan-12β-ol	182
trans-1-Decalone	—	—	—	—	PtO_2/AcOH/HCl	*trans,cis*-1-Decalol (*trans,cis*:*trans,trans* = 89:11)	197
2-Methylcyclohexanone	3.1	17.3	15	85	Pt/AcOH/HCl	*cis*-2-Methylcyclohexanol (cis:*trans* = 93:7)	198
					RaNi/EtOH/ NaOH	*cis*-2-Methylcyclohexanol (*cis*:*trans* = 80:20)	153c
3,3,5-Trimethylcyclohexanone	2.7	52.6	5	95	PtO_2/MeOH	*trans*-3,3,5-Trimethylcyclohexanol (*trans*:*cis* = 91:9)	153a
					Nic/EtOH	*trans*-3,3,5-Trimethylcyclohexanol (*trans*:*cis* = 95:5)	199
2-Methylcyclopentanone	3.6	17.2	17	83	Pt/AcOH/HCl	*cis*-2-Methylcyclopentanol (*cis*:*trans* = 65:35)	153b
					RaNi/EtOH	*cis*-2-Methylcyclopentanol (*cis*:*trans* = 80:20)	177

[a]Wipke, W. T.; Gund, P. *J. Am. Chem. Soc.* **1976**, *98*, 9107. Reprinted with permission from American Chemical Society. Overt—least congested side of ketone; covert—most congested side of ketone.
[b]At atmospheric hydrogen pressure unless otherwise noted.
[c]At 0.34 MPa H_2.
[d]At 6.9–9.8 MPa H_2.
[e]The structure of the 11-one really hydrogenated is not certain.



Scheme 5.12 Hydrogenation of D-fructose.

and co-workers on the hydrogenation of β-keto esters to optically active β-hydroxy esters.[206] Raney nickel catalyst modified by optically active tartaric acid has been found to be effective for the hydrogenation of methyl acetoacetate to optically active 3-hydroxybutyrate.[207] Later studies have revealed that to obtain a high optical yield use of reduced nickel oxide or Ni–Pd–kieselguhr modified with tartaric acid is effective.[208,209] Thus, optically active ethyl 3-hydroxybutyrate was obtained in an 81.7% ee (enantiomeric excess) from the corresponding keto ester over reduced nickel oxide modified by tartaric acid with addition of a small amount of acetic acid.[208] Similarly, optically active methyl β-hydroxybutyrate was obtained in 90.6% ee over Ni–Pd–kieselguhr modified by tartaric acid with addition of a small amount of formic acid (eq. 5.47).[209] The optical yields given above are those corrected on the basis of a newly estimated value of $[\alpha]_D^{20} = -22.95°$ (neat) for pure methyl (*R*)-3-hydroxybutyrate.[210]

$$\underset{23.5\text{ g }(0.2\text{ mol})}{CH_3COCH_2CO_2Me} \xrightarrow[\substack{44\text{ ml THF/1.1 mmol }HCO_2H \\ 98\text{–}100°C,\ 8.3\text{–}6.9\text{ MPa }H_2,\ 24\text{ h}}]{2.3\text{ g Ni–Pd–kieselguhr }(1:0.01:1)^*} \underset{[a]_D^{20} = -20.79°\ (90.6\%\text{ ee})}{CH_3CHOHCH_2CO_2Me} \quad (5.47)$$

* Modified by 1.5% aq. solution of (*R,R*)-tartaric acid at pH 4.3 and 83–85°C.

Later, the optical yields over the modified Raney Ni were greatly improved by hydrogenating the substrate in the presence of sodium bromide.[210] Thus, the best optical yield of 88.6% ee was obtained in the hydrogenation of methyl acetoacetate over Raney Ni modified 3 times with tartaric acid in the presence of sodium bromide with addition of a small amount of acetic acid (eq. 5.48).

$$\underset{11.5\text{ ml}}{CH_3COCH_2CO_2Me} \xrightarrow[\substack{23\text{ ml }C_2H_5CO_2Me,\ 0.2\text{ ml AcOH} \\ \text{RT to }100°C,\ 8.8\text{ MPa }H_2,\ <10\text{ h}}]{0.8\text{ g Raney Ni}^*} \underset{[\alpha]_D^{20} = -20.34°\ (88.6\%\text{ ee})}{CH_3CHOHCH_2CO_2Me} \quad (5.48)$$

* Modified by a solution of 1 g (*R,R*)-tartaric acid and 10 g NaBr in 100 ml H_2O at pH 3.2 3 times.

4-Hydroxy-2-butanone and its methyl ether were also hydrogenated in 69 and 68% ee, respectively, using the same modified nickel catalyst.[211] Acetylacetone was first hydrogenated to (*R*)-4-hydroxy-2-pentanone in 87% ee over the Raney Ni modified by (*R,R*)-tartaric acid. Then the (*R*)-hydroxy ketone was hydrogenated to a mixture of

78.3% of (*R*,*R*)-2,4-pentanediol and 8.7% of (*R*,*S*)-2,4-pentanediol. The results indicate that the hydrogenation of the (*R*)-hydroxy ketone to the (*R*,*R*)-diol was highly diastereoselective (90%).[212] The presence of an appreciable amount of carboxylic acid was favorable for obtaining high optical yields in enantioselective hydrogenation of various alkyl methyl ketones over the modified Raney Ni.[213] The highest optical yield of 74% was obtained in the hydrogenation of 3,3-dimethyl-2-butanone in the presence of pivalic acid.

Later detailed studies revealed that the enantioselectivity of the Raney Ni is improved by removing the aluminum-rich component from the surface of the catalyst, as has been effectuated by treating the catalyst repeatedly with tartaric acid. The adsorbed tartaric acid was found to be effective only when it existed as a mono- or disodium salt, and free tartaric acid or its salts of lithium, potassium, magnesium, and aluminum were not effective.[214] Tai et al. have prepared an improved asymmetrically modified Raney Ni by ultrasonic irradiation of Raney Ni in water followed by removal of the resulting turbid supernatant suspension by decantation.[215] It has been shown that the aluminum-rich part of Raney Ni is thus removed effectively by analysis of the solid materials collected from the supernatant suspension. By modifying the Raney Ni thus pretreated with optically active tartaric acid and sodium bromide, high enantioselectivities and activities have been obtained in the hydrogenation of 1,3-diketones and 3-oxoalkanoic esters. With use of this improved modified catalyst, the reaction time was shortened by a factor of 2–4 and the optical yield improved by 5–8% in comparison with the previous modified Raney Ni in the hydrogenation of methyl 3-oxoalkanoates. The highest optical yield (94%) was obtained in the hydrogenation of methyl 3-oxotetradecanoate at 100°C and 9.8 MPa H_2. The hydrogenation of acetylacetone gave (*R*,*R*)-2,4-pentanediol in 91% optical yield. More than 98% optical yield has been reported in the hydrogenation of methyl 3-cyclopropyl-3-oxopropanoate.[216]

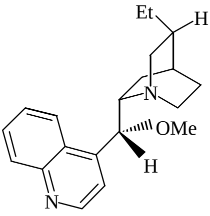
Orito et al. were successful for the hydrogenation of α-keto esters to optically active α-hydroxy esters using Pt–C or Pt–Al_2O_3 modified with quinine or cinchonidine as the catalyst.[217,218] Usually higher optical yields were obtained over the modified Pt–Al_2O_3 than over the modified Pt–C. Thus, methyl pyruvate was hydrogenated to methyl (*R*)-(+)-lactate in 86.8% ee over 5% Pt–Al_2O_3 modified with quinine (eq. 5.49). Ethyl benzoylformate was likewise hydrogenated to ethyl (*R*)-(−)-mandelate in 83.9% ee in benzene over 5% Pt–Al_2O_3 modified with cinchonidine at room temperature and 4.9 MPa H_2.

$$\underset{12.3\ \text{ml}}{CH_3COCO_2Me} \xrightarrow[\text{RT, 6.9 MPa } H_2\text{, <1 h}]{\text{0.5 g 5\% Pt–}Al_2O_3\text{*}\ /\ \text{24 ml benzene/0.1 g quinine}} \underset{[\alpha]_D^{20} = +7.16°\ (86.8\%\ ee)}{CH_3CHOHCO_2Me} \qquad (5.49)$$

* Preheated at 400°C under H_2 and modified by 1% EtOH solution of quinine at RT.

Later studies by Blaser et al. revealed that the enantioselectivities as well as the rates of hydrogenation for α-keto esters are increased by hydrogenation in acetic acid. In the hydrogenation of ethyl pyruvate the best results (93–95% ee) were obtained in ace-

tic acid, using a special wide-pore Pt–Al_2O_3 catalyst and 10,11-dihydro-*O*-methylcinchonidine (**30**) as modifier (eq. 5.50).[219] It is of interest that the modification with cinchona alkaloids leads to a marked increase in reaction rate.[220] Similarly, ethyl 4-phenyl-2-oxobutyrate was hydrogenated to give the corresponding optically active hydroxybutyrate in 91% ee at 10°C. It is noted that the platinum catalyst modified with the cinnconidinium chlorides quaternarized with methyl or benzyl groups in the aliphatic nitrogen are completely ineffective for enantioselective hydrogenation.[221]



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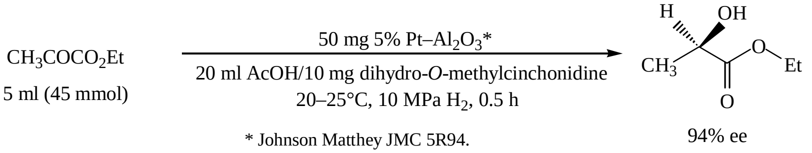
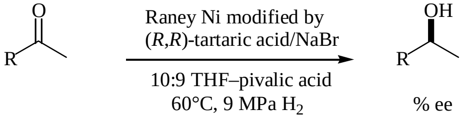


(5.50)

Blaser and Jalett obtained moderate to good (>80%) optical yields in enantioselective hydrogenation of α-keto acids using platinum catalysts modified with cinchona alkaloids. In contrast to the cases with α-keto esters, high optical yields were obtained by hydrogenation in aqueous alcohols. The best results were obtained in hydrogenation with a combination of Pt–Al_2O_3 (Johnson Matthey 5R94) and **30** in EtOH/10% H_2O at 25–30°C and 7–10 MPa H_2, which led to an 85% ee with 4-phenyl-2-oxobutyric acid and a 79% ee with pyruvic acid.[222]

Minder et al. studied various modifiers containing a nitrogen base for the enantioselective hydrogenation of ethyl pyruvate.[223,224] Up to 82% ee with (*R*)-1-(1-naphthyl)ethylamine and up to 75% ee with (*R*)-2-(1-pyrrolidinyl)-1-(1-naphthyl)-ethanol as modifiers were achieved in the hydrogenation of ethyl pyruvate to (*R*)-ethyl lactate over Pt–Al_2O_3 in acetic acid.

Simple 2-alkanones, which usually afford optically active alcohols only in low optical yields with modified Raney Ni, have been converted to active alcohols in 72–85% ee by hydrogenation over the Raney Ni modified with optically active tartaric acid and sodium bromide in the presence of an excess amount of pivalic acid (eq. 5.51).[225–227] In the absence of pivalic acid the optical yield was negligible in the hy-



R	% ee
R = Et	72
= *i*-Pr	85
= hexyl	80

(5.51)

drogenation of 2-octanone. The optical yield in the presence of pivalic acid increased with decreasing reaction temperatures from 180°C to 50–60°C. The mechanism of heterogeneous enantioselective hydrogenations has been discussed by Sutherland et al.,[228] Augustine et al.,[229] Simons et al.,[230] Schwalm et al.,[231] and Margitfalvi et al.[232]

5.5 MECHANISTIC ASPECTS OF THE HYDROGENATION OF KETONES

Tanaka has recently reviewed the hydrogenation of ketones with an emphasis on the mechanistic aspects of the reaction.[233] Numerous references related to this subject can be found in his article. Deuteration of cyclohexanones and an application of NMR spectroscopy to the analysis of deuterated products have revealed that on ruthenium, osmium, iridium, and platinum, deuterium is simply added to adsorbed ketones to give the corresponding alcohols deuterated on the C1 carbon, without any deuterium atom at the C2 and C6 positions, while over palladium and rhodium the C2 and C6 positions are also deuterated.[234] A distinct difference between rhodium and palladium is that on rhodium deuterium is incorporated beyond the C2 and C6 positions whereas on palladium the distribution of deuterium is limited to the C2 and C6 carbons.[234,235] From these results, together with those on the deuteration of adamantanone,[236] it has been concluded that a π-oxaallyl species is formed on palladium while deuterium may be propagated by an α,β process[237] on rhodium via a staggered α,β-diadsorbed species.

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CHAPTER 6

Preparation of Amines by Reductive Alkylation

An aldehyde or ketone may react with ammonia or a primary or secondary amine to give alkylated amines in the presence of catalyst under hydrogenation conditions. The reaction that was first described by Mignonac[1] has been widely applied to the preparation of various amines and is known as the *reductive alkylation* of ammonia and amines or the *reductive amination* of aldehydes and ketones.[2] Alcohols may also react with primary and secondary amines in the presence of hydrogenation catalysts such as nickel, palladium, and copper–chromium oxide to give secondary and tertiary amines.[3] Since amines are seldom alkylated with tertiary alcohols, alkylation is believed to occur by the reaction of the aldehyde or ketone, formed by dehydrogenation on the catalyst, with amines. As is expected, the reaction of amines with alcohols requires much higher temperatures (180°C or higher over Raney Ni and Cu–Cr oxide) and longer reaction times than the reaction with the carbonyl compounds.[3]

6.1 REDUCTIVE ALKYLATION OF AMMONIA WITH CARBONYL COMPOUNDS

Reductive alkylation of ammonia may proceed under mild conditions over nickel catalysts. In examples using Raney Ni, temperatures ranging from 40 to 150°C and hydrogen pressures of 2–15 MPa have been used to obtain satisfactory results.[3,4] In general, the reductive alkylation of ammonia with carbonyl compounds may produce primary, secondary, and tertiary amines, as well as an alcohol, a simple hydrogenation product of the carbonyl compound (Scheme 6.1). The selectivity to respective amine depends primarily on the molar ratio of the carbonyl compound to ammonia, although the nature of catalyst and structure of the carbonyl compound are also important factors for the selectivity. As an example, the reaction of benzaldehyde in the presence of 1 equiv of ammonia in ethanol over Raney Ni gave benzylamine in an 89.4% yield while with 0.5 molar equivalent of ammonia dibenzylamine was obtained in an 80.8% yield (eq. 6.1).[4]

$$\text{PhCHO} + \text{NH}_3 \xrightarrow[\text{300 ml EtOH*, 40–70°C, 9 MPa H}_2]{\text{10 g Raney Ni}} \text{PhCH}_2\text{NH}_2 + (\text{PhCH}_2)_2\text{NH} \qquad (6.1)$$

PhCHO	NH_3	$PhCH_2NH_2$	$(PhCH_2)_2NH$
318 g (3 mol)	51 g (3 mol)	89.4%	7.1%
318 g (3 mol)	25.5 g (1.5 mol)	11.8%	80.8%

* The aldehyde was added to a solution of ammonia in cooled ethanol.

$$RCOR' + NH_3 \xrightarrow{H_2} RR'CHNH_2 + H_2O$$

$$2\,RCOR' + NH_3 \xrightarrow{2H_2} (RR'CH)_2NH + 2\,H_2O$$

$$3\,RCOR' + NH_3 \xrightarrow{3H_2} (RR'CH)_3N + 3\,H_2O$$

$$RCOR' \xrightarrow{H_2} RR'CHOH$$

(R' = H or alkyl)

Scheme 6.1 Products of the reductive alkylation of ammonia with an aldehyde or ketone.

With aliphatic aldehydes having α-hydrogen atoms, especially of the type RCH_2CHO, the yields of the corresponding alkylamines may be lowered with the formation of tarry byproducts through the aldol or other condensation reactions. Further, reductive alkylation with lower aliphatic aldehydes tends to give a mixture of primary, secondary, and tertiary amines. Butyraldehyde ammonia hydrate, butyraldehyde in an alcoholic solution of ammonia, and heptanal ammonia were converted into compounds of relatively high molecular weight to the extent of 47–55% in the hydrogenation over Ni–kieselguhr at 100–125°C and 10–15 MPa H_2.[5] The yields of primary amines were 32–36% and those of secondary amines, 12–26%. With butyraldehyde ammonia hydrate, 32% of butylamine, 12% of dibutylamine, and 23% of 2-propyl-3,5-diethylpyridine, as one of high-molecular-weight condensation products, were isolated, although Mignonac obtained a 68% of butylamine at low-pressure hydrogenation of butyraldehyde in aqueous ammonia over a nickel catalyst. The reaction of butyraldehyde with 0.5 equiv of ammonia over Raney Ni also resulted in a mixture of 31% of butylamine, 17% of dibutylamine, and 8% tributylamine.[6] Heptanal was converted to heptylamine in 59%[3] and 53–63% yields in the presence of excess ammonia in methanol over Raney Ni (eq. 6.2).[7]

$$\underset{320\text{ g }(2.8\text{ mol})}{CH_3(CH_2)_5CHO} \xrightarrow[\substack{500\text{ ml MeOH/150 ml (6.4 mol) liq. }NH_3\\ 150°C,\ 34.5\text{–}24\text{ MPa }H_2}]{1\text{ tablespoon Raney Ni}} \underset{53\text{–}63\%}{CH_3(CH_2)_5CH_2NH_2} \qquad (6.2)$$

Caproaldehyde (hexanal), pelargonaldehyde (nonanal), and azelaaldehydic esters (8-alkoxycarbonyloctanals) were converted to the corresponding primary amines in high yields in the presence of a large excess of ammonia over Raney Ni.[8] In particular, methyl 9-aminononanoate was formed in 97.2% yield (GC) from methyl azelaaldehydate in the presence of a 20-fold excess of ammonia over Raney Ni in heptane–methanol at 75°C and 6.9 MPa H_2 (eq. 6.3). The only other product detected was 2.8% of methyl 9-hydroxynonanoate. It has been suggested that the use of the two immiscible solvents led to the high yield of the amino compound.

$$\mathrm{OHC(CH_2)_7CO_2Me} \xrightarrow[\substack{\text{heptane/MeOH} \\ \text{20-fold molar excess } NH_3 \\ 75^\circ C,\ 6.9\ \text{MPa}\ H_2}]{\text{Raney Ni}} \underset{97.2\%\ (GC)}{\mathrm{H_2N(CH_2)_8CO_2Me}} + \underset{2.8\%\ (GC)}{\mathrm{HO(CH_2)_8CO_2Me}} \quad (6.3)$$

The reaction of nonanal with 0.5 equiv of ammonia gave dinonylamine in 81% yield (GC) along with small amounts of nonylamine, trinonylamine, and 1-nonanol over Raney Ni in heptane/methanol at 75°C and 6.9 MPa H_2, while substitution of Pd–C for the nickel catalyst and omission of solvent resulted in the formation of trinonylamine as the predominant product (eq. 6.4). It is noted that hydrogenation of the stoichiometric 3:1 aldehyde–ammonia mixture resulted in decreased yield of trinonylamine (73.2%) accompanied by the formation of 1-nonanol in an amount of 20.0%.

$C_8H_{17}CHO$	+ 29.9% aq. NH_3	⟶	$C_9H_{19}NH_2$	+ $(C_9H_{19})_2NH$	+ $(C_9H_{19})_3N$	+ $C_9H_{19}OH$
25 g (0.176 mol)	5.75 ml (0.0905 mol)	3 g Raney Ni*	5.4%	81.0%	3.2%	8.7%‡
10 g (0.0703 mol)	2.30 ml (0.036 mol)	1 g 10% Pd–C†	3.7%	6.8%	84.1%	0.0%§

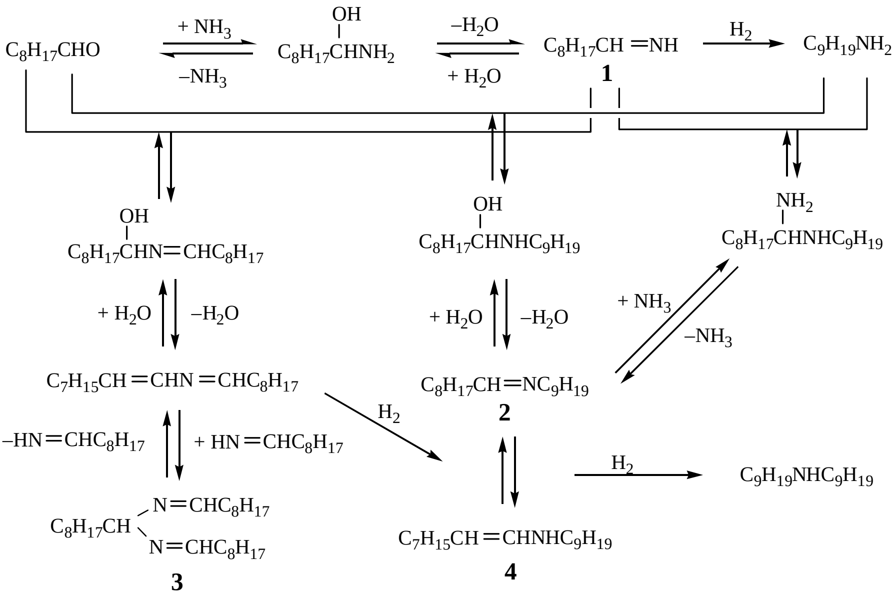
* Solvent: 75 ml heptane–75 ml MeOH; 75°C; 6.9 MPa H_2; 4 h.
† No solvent; 100°C; 6.9 MPa H_2; 4 h.
‡Plus 1.7% of other product.
§ Plus 5.4% of other product.
(6.4)

Yada et al. investigated the reductive amination of nonanal in the presence of a large excess of ammonia (molar aldehyde/ammonia ratio = 1: 9.4) over group VIII (groups 8–10) metals in ethanol at 50°C and 8 MPa H_2.[9] As seen from the results shown in Table 6.1, the yield of nonylamine increased with respect to catalyst metal in the following order: Pd < Os < Pt < Rh < Ir < Ru = Raney Ni < Raney Co. The highest yield (94%) of nonylamine was obtained with Raney Co. Over ruthenium and Raney Ni the yield decreased to 87%, due to the formation of dinonylamine and 1-nonanol, respectively. On the other hand, over palladium and osmium dinonylamine was produced in larger amounts than nonylamine, while trinonylamine was found only in small amounts (6% and 1%, respectively). In general, the formation of primary amine did not increase with the addition of ammonium chloride, although it was reported to be effective for the conversion of some ketones to primary amines over platinum.[10] On the other hand, the formation of tertiary amine over palladium increased from 6 to 45% in the presence of ammonium chloride. The maximum amount of the Schiff base, *N*-nonylidenenonylamine (**2**), found as an intermediate during the reaction, was 69% over Raney Ni, 67% over Raney Co, and 53% over ruthenium, which were in all cases much greater than the amounts of secondary amine produced over the respective metal. These results indicate that the reaction pathways leading to the formation of primary amine involve the decomposition of **2** formed as an intermediate into nonylamine and 1-nonanimine (**1**) in the presence of ammonia (see Scheme 6.2).[11] Significant amounts of *N,N*-dinonyl-1-nonenylamine (**5**), a tertiary amine precursor (see Scheme 6.3), were also found as an intermediate during the reaction even when no tertiary amine was formed. Similar to **2**, the tertiary amine precursor **5** also appears to be decomposed into the secondary amine and 1-nonanimine in the presence of ammonia (Scheme 6.3). The hydroamide *N,N′*-dinonylidene-1,1-nonanediamine

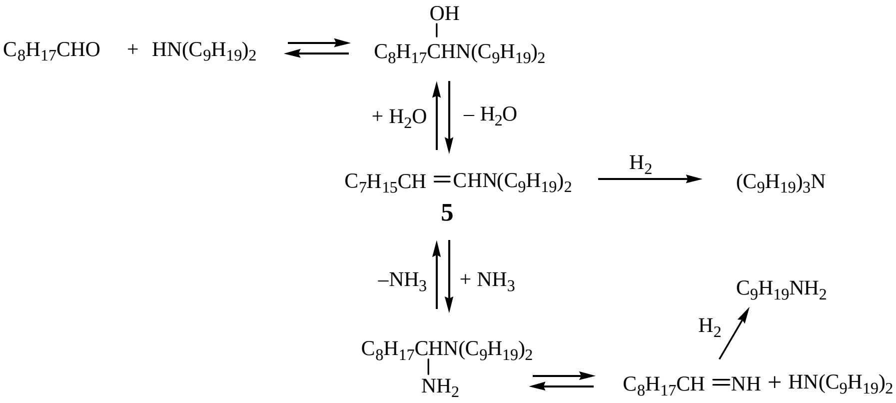
TABLE 6.1 Reductive Alkylation of Ammonia with Nonanal[a,b]

Catalyst	Conversion (%)	Yield of Product (%)[c] Nonylamine	Dinonylamine	Trinonylamine	1-Nonanol	Schiff base[d]
Pd	95	24	62	6	0	3
Ru	97	87	10	0	0	0
Rh	99	52	46	0	1	0
Pt	89	48	33	0	2	6
Ir	97	66	28	0	1	2
Os	99	35	53	1	10	0
Raney Co	100	94	6	0	0	0
Raney Ni	100	87	2	0	11	0

[a]Data of Yada, S.; Takagi, Y.; Hiyamizu, M. *Nippon Kagaku Kaishi* **1995**, 107. Reprinted with permission from Chemical Society of Japan.
[b]Nonanal (0.71 g, 0.005 mol) was hydrogenated in the presence of 0.8 g (0.047 mol) of ammonia in 10 ml of ethanol over 0.01 g of platinum metal or 0.5 g of Raney catalyst at 50°C and 8 MPa H_2 for 24 h.
[c]Analyzed by GC.
[d]*N*-Nonylidenenonylamine.



Scheme 6.2 Reactions of nonanal in the presence of ammonia and hydrogen leading to the formation of nonylamine and dinonylamine.

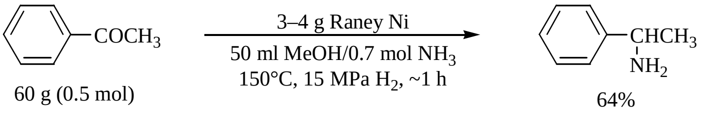


Scheme 6.3 The formation and reactions of trinonylamine precursor **5** in the presence of ammonia and hydrogen.

(**3**), although not detected over Raney Ni and Raney Co, was found over ruthenium and palladium at initial stages of the reaction, although it was transformed into other products more rapidly than the Schiff base **2**. On the basis of these results, the reaction pathways leading to the formation of the intermediates as well as to the primary, secondary, and tertiary amines are formulated as in Schemes 6.2 and 6.3.[9] The selectivity of catalyst metals for the formation of primary and secondary amines has been discussed by Yada et al. on the basis of the reaction pathways that involve the isomerization of the Schiff base **2** to the enamine **4**, which may explain the extensive formation of secondary amine over palladium.[9]

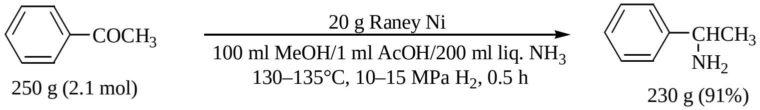
The reductive alkylation of ammonia with ketones is performed under conditions similar to those for aldehydes, but appears to proceed with more difficulty. Skita and Keil obtained only about 30% yields of primary amine from acetone and 2-butanone in hydrogenation over a nickel catalyst in water containing slightly excessive molar ratios of ammonia at 90°C and 2 MPa H_2, although primary amines were usually obtained in fair to good yields from most ketones.[12] Cyclohexylamine was obtained in ~50% yield in 50% ethanol–water solution under otherwise identical conditions, although ~80% yields were reported by other investigators.[1,13] Rhormann and Shonle obtained 2-aminoheptane in 75–80% yield by reductive amination of 2-heptanone in absolute ethanol saturated with dry ammonia at –10°C over Raney Ni at 75–80°C and 10 MPa H_2.[14] Schwoegler and Adkins hydrogenated various ketones over Raney Ni in the presence of 1.4 equiv of ammonia to ketone in methanol at 150°C and 15 MPa H_2 and obtained the corresponding primary amines in yields of 65% with 3-methyl-2-butanone, 51% with 3,3-dimethyl-2-butanone, 48% with 2,4-dimethyl-3-pentanone, 72% with 5-nonanone, 64% with acetophenone (eq. 6.5), and 19% with benzophenone.[3] Acetonylacetone under the same conditions gave 2,5-dimethylpyrrolidine and 2,5-dimethylpyrrole in 28 and 59% yields, respectively, while acetylacetone underwent ammonolysis to give acetamide in quantitative yield.[3] Somewhat

lower yields of 1-phenylethylamine (44–52%) from acetophenone and 50–55% yields of 2-aminoheptane from 2-heptanone were reported in the hydrogenation over Raney Ni in a 5-fold excess liquid ammonia at 150°C and 34.5–24 MPa H_2.[7]



(6.5)

The yields of primary amines over platinum oxide were improved in the presence of an excess molar equivalent of ammonium chloride in low pressure reductive alkylation of ammonia with ketones in methanol saturated with ammonia.[10] With acetophenone and 4-methyl-2-pentanone, the yields of primary amine increased from 37 and 49% in the absence of ammonium chloride to 69 and 57–65%, respectively, in the presence of ammonium chloride. Möller obtained a much higher yield (>90%) of 1-phenethylamine from acetophenone by adding a small amount of acetic acid to methanol–ammonia with Raney Ni (eq. 6.6).[15] The reductive amination of benzophenone in the presence of Raney Co and some ammonium acetate gave ~70% yield of benzohydrylamine, compared to only 19% under usual conditions with Raney Ni.[3]



(6.6)

Gobolos et al. studied reductive amination of acetone with ammonia in a flow system at 169–210°C and 0.8 MPa H_2 ($H_2/NH_3 = 0.5$) on Raney Ni that had been modified by organic tin compounds with general formula of SnR_nCl_{4-n} (R = Et, Bu, or benzyl) in order to suppress the formation of isopropyl alcohol.[16] By introducing tin from tetraalkyl tin, the selectivity to the formation of secondary amine significantly increased at the expense of the primary amine (isopropylamine/diisopropylamine ratio = 68.2/24.1 at 192°C, compared to 83.6/8.6 at 190°C with unmodified catalyst). By modifying the catalyst with $SnBzl_2Cl_2$, the lowest selectivity (<1%) for the formation of isopropyl alcohol was obtained at temperatures of 171–202°C. The isopropylamine/diisopropylamine ratio was close to the values obtained on the unmodified catalyst (7.3% selectivity to isopropyl alcohol at 190°C).

Dialkyl ketones, especially sterically hindered ones, tend to give the corresponding alcohols to significant extents under conditions of reductive amination, resulting in lower yields of amines. As in the cases of the aromatic ketones described above, the addition of small amounts of acetic acid or ammonium acetate is effective to depress the formation of alcohols, which may become a significant side reaction over those catalysts that are active for the hydrogenation of ketones to alcohols such as ruthenium, Raney Co, and Raney Ni.[17] Thus, the formation of 2-nonanol could be depressed effectively in the presence of ammonium acetate in the reductive amination of 2-nonanone over these catalysts (eq. 6.7).

$$\underset{0.71\ \text{g}\ (0.005\ \text{mol})}{CH_3COC_7H_{15}} \xrightarrow[\text{50°C, 8 MPa } H_2]{\text{10 ml EtOH/0.8 g (0.047 mol) } NH_3} CH_3CH(NH_2)C_7H_{15} + CH_3CHOHC_7H_{15} \tag{6.7}$$

Catalyst (g)	NH_4OAc (g)		
Ru, 0.01	—	75 (%)	25 (%)
Ru, 0.01	0.2	93	7
Raney Co, 0.5	—	67	33
Raney Co, 0.5	0.2	98	2
Raney Ni, 0.5	—	46	54
Raney Ni, 0.5	0.2	100	0

In the reductive alkylation of ammonia with cyclohexanone, Skita and Keil found that, although cyclohexylamine was obtained in 50% yield over a nickel catalyst, over colloidal platinum dicyclohexylamine was produced as the predominant product even in the presence of an excess molar equivalent of ammonia. Steele and Rylander compared the selectivity to primary amine, secondary amine, and alcohol in the reductive alkylation of ammonia with 2- and 4-methylcyclohexanones over 5% Pd-, 5% Rh-, and 5% Ru-on-carbon as catalysts.[18] As seen from the results shown in Table 6.2, the formation of secondary amine is greatly depressed by the methyl group at the 2 position. Thus over Pd–C the secondary amine was formed predominantly with cyclohexanone and 4-methylcyclohexanone while the primary amine was produced in 96% selectivity with 2-methylcyclohexanone. Over Ru–C the alcohol was formed quantitatively with 4-methylcyclohexanone without the formation of any amines, whereas with 2-methylcyclohexanone the alcohol was formed only to an extent of 57%, accompanied by the formation of 4 and 39% of the secondary and primary amines, respectively. These results indicate that secondary amine formation is affected by the steric hindrance of the methyl group to a much greater extents than is the formation of the primary amine or the alcohol. The results with Ru–C and Rh–C also indicate

TABLE 6.2 Reductive Alkylation of Ammonia with Cyclohexanones[a,b]

			Product (wt%)		
Catalyst	Cyclohexanone	Molar Ratio of NH_3 to Ketone	Cyclohexylamine	Dicyclohexylamine	Cyclohexanol
5% Rh–C	4-Methyl-	6	44	40	16
5% Ru–C	4-Methyl-	6	0	0	100
5% Pd–C	4-Methyl-	6	27	72	1
5% Pd–C	4-Methyl-	1.25	8	91	1
5% Rh–C	2-Methyl-	6	80	0	20
5% Ru–C	2-Methyl-	6	39	4	57
5% Pd–C	2-Methyl-	6	96	3	1
5% Pd–C	Unsubstituted	6	4	96	0

[a] Steele, D. R.; Rylander, P. N. in Rylander, P. N. *Catalytic Hydrogenation over Platinum Metals*; Academic Press: New York, 1967; p 292. Reprinted with permission from Academic Press Inc.
[b] Temperature, 100°C; H_2 pressure, 6.9 MPa; no solvent; ammonia present as concentrated aqueous solution.

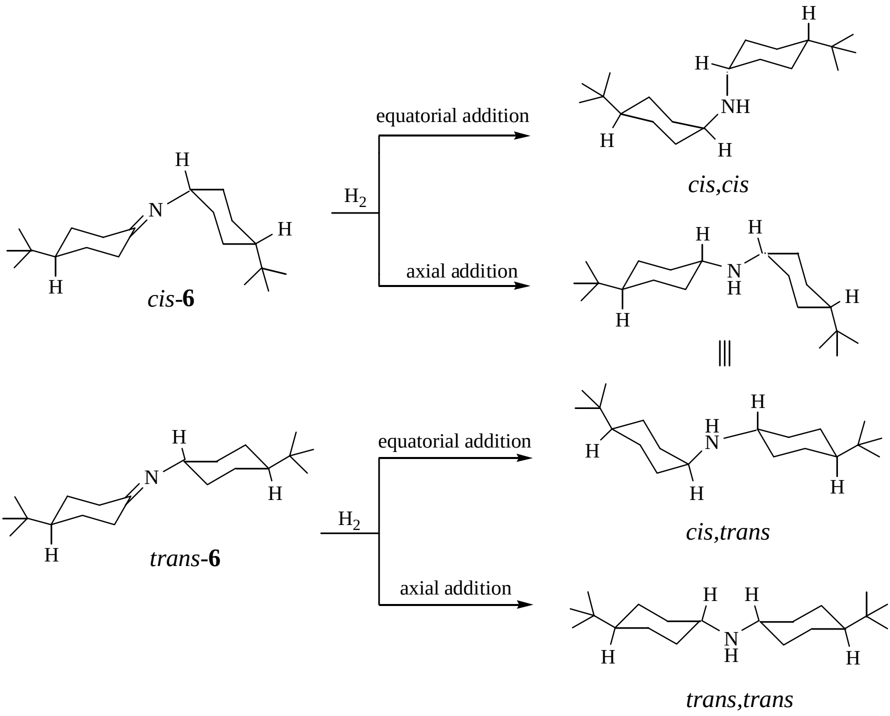
that the primary amine formation is depressed by the steric hindrance to a lesser extent than is the alcohol formation. Under the conditions of the reaction, Pt–C was rapidly poisoned.

Yada et al. studied the selectivity as well as the stereochemistry of the reductive alkylation of ammonia with 4-*t*-butylcyclohexanone over the six platinum metals in ethanolic ammonia (about 3.5:1 molar ratio of NH_3: ketone) at 50°C and 7.8 MPa H_2 (Table 6.3).[19] The selectivity to the primary amine, which was always higher than that to the secondary amine, was the highest with ruthenium (97%), while the selectivity to the secondary amine was the highest over platinum (34%). Over all the metals the *cis* isomer and the *cis–cis* isomer were predominant in the formation of the primary and secondary amines, respectively. The results on the hydrogenation of stereoisomeric mixtures of the azomethine, *N*-(4-*t*-butylcyclohexylidene)-4-*t*-butylcyclohexylamine, (*cis*- and *trans*-**6**, Scheme 6.4) indicated that the addition of hydrogen to the C=N bond occurred almost exclusively (91–100%) from the equatorial side. The formation of the alcohol was always at low levels (0–9%). Over ruthenium and palladium, the maximum amounts of the azomethine **6** formed as an intermediate during the reaction were greater than the amounts of the secondary amine finally produced, while over platinum the azomethine **6** was formed in a lesser amount than the secondary amine. The results with ruthenium and palladium catalysts indicate that **6** formed as an intermediate is decomposed to give the primary amine in the presence of ammonia, similarly as in the reductive amination of nonanal (cf. Schemes 6.2 and 6.3). In fact, the hydrogenation of **6** over ruthenium in the presence of ammonia gave 95% of the primary amine and only 5% of the secondary amine, while in the absence of ammonia **6** was hydrogenated to the secondary amine quantitatively. Over platinum the

TABLE 6.3 Reductive Alkylation of Ammonia with 4-*t*-Butylcyclohexanone over Platinum Metals[a,b]

Catalyst	Reaction Time (h)	Primary Amine[c] Yield (%)	Primary Amine[c] *cis*: *trans*	Secondary Amine[d] Yield (%)	Secondary Amine[d] *cis,cis*: *cis,trans*: *trans,trans*	Alcohol (%)[e]
Ru	9	97	77: 23	0	—	3
Rh	3	95	88: 12	4	—	1
Pd	4	90	79: 21	10	68: 32: 0	0
Pt	2	59	63: 37	34	51: 46: 3	7
Os	16	74	82: 18	17	68: 32: 0	9
Ir	5	88	66: 34	11	70: 30: 0	1

[a]Data of Yada, S.; Yazawa, N; Yamada, Y.; Sukegawa, S.; Takagi, Y. *Nippon Kagaku Kaishi* **1989**, 641. Reprinted with permission from Chemical Society of Japan.
[b]4-*t*-Butylcyclohexanone (0.77 g, 0.005 mol) was hydrogenated over 0.01 g of metal black in 10 ml ethanol containing about 0.3 g (0.0176 mol) of ammonia at 50°C and 7.8 MPa H_2.
[c]4-*t*-Butylcyclohexylamine.
[d]Bis(4-*t*-butylcyclohexyl)amine.
[e]4-*t*-Butylcyclohexanol.

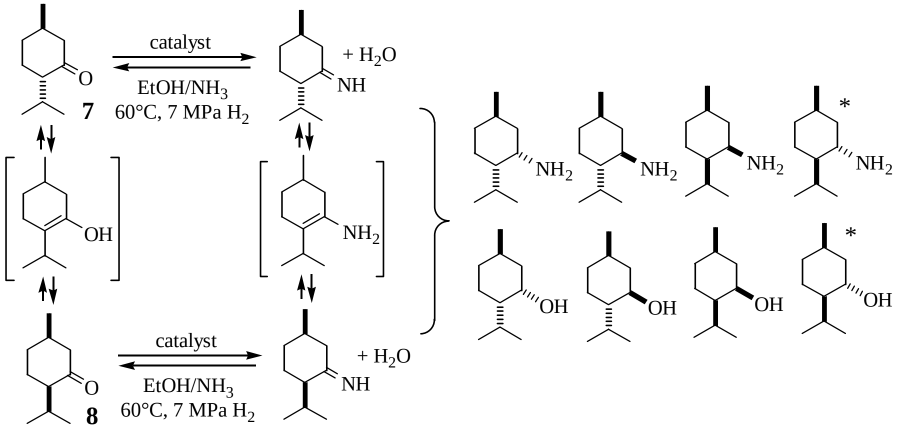


Scheme 6.4 Stereochemistry of the hydrogenation of *cis*- and *trans*-*N*-(4-*t*-butylcyclohexylidene)-4-*t*-butycyclohexylamine.

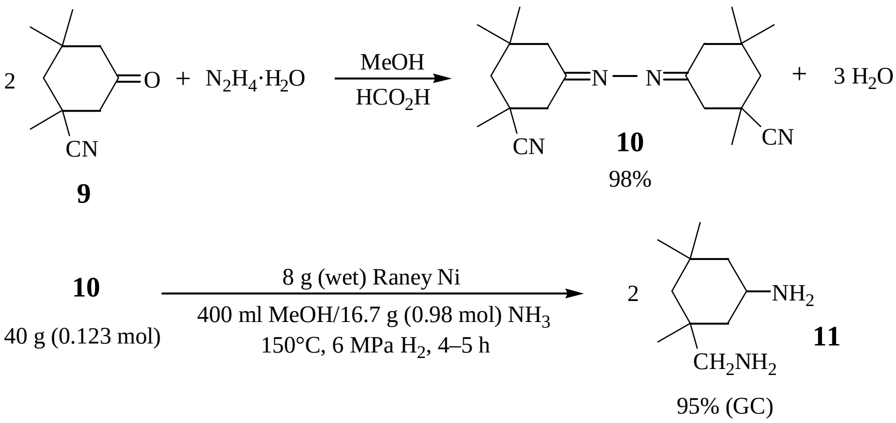
azomethine **6** appears to be hydrogenated rapidly without being accumulated in a greater amount than the secondary amine. Even over platinum, 69% of the primary amine was formed along with 31% of the secondary amine from the azomethine in the presence of ammonia. Yada and Takagi also studied the reductive amination of menthone (**7**) and isomenthone (**8**) over four platinum metals supported on carbon as well as over Raney Ni and Raney Co under similar conditions as for 4-*t*-butylcyclohexanone.[20] In line with the results by Steele and Rylander (Table 6.2), the formation of secondary amine was completely depressed with these hindered ketones. The selectivity to the primary amines, however, was decreased by concurrent formation of the alcohols, which greatly depended on the catalyst: none (0%) over Pd–C and as great as 61.7% over Pt–C with menthone. The selectivity to the primary amines (see figures in parentheses) decreased in the following order with respect to the catalyst: 5% Pd–C (100%) > 5% Ru–C (96.5%) > 5% Rh–C (90.2%) > Raney Co (61.7%) > Raney Ni (51.1%) > 5% Pt–C (38.3%). The formation of stereoisomeric products in the amine and alcohol products as well as the presence of isomenthone in unreacted menthone indicated that the isomerization of menthone to isomenthone and/or the isomerization of the corresponding imine occurred extensively during the reductive amination prob-

ably through the reactions shown in Scheme 6.5. Since the rate of reductive amination of **8** was much smaller than that for **7**, a significant part of the products from **8** appears to be formed through **7**.

In a process for the synthesis of isophoronediamine (3-aminomethyl-3,5,5-trimethylcyclohexylamine) (**11**), which finds an expanding demand on the market such as in the manufacture of polyurethanes, paints, and vanishes, isophoronenitrile (**9**) was aminated through the reaction with hydrazine to give bis(3-cyano-3,5,5-trimethylcyclohexylidene)azine (**10**) followed by hydrogenation of the azine with Raney Ni or Raney Co (Scheme 6.6). In this manner the formation of byproducts such as amino alcohol, azabicyclic compound, or the secondary amine could be minimized, and isophoronediamine was obtained in 90–95% overall yields.[21] Analysis of the reaction mixture in the course of the hydrogenation of **10** indicated that **10** was rapidly hydrogenated at the nitrile group to give the azine with two aminomethyl groups, which was further hydrogenated to **11**, probably through the corresponding hydrazine, although it was not observed during the hydrogenation. The *cis/trans* isomer ratio of **11**, obtained thus via the azine, was 44/56 over Raney Ni and 49.5/50.5 over Raney Co, which were quite different from that obtained by the usual amination of **9** (about 80/20). In a patent, isophoronenitrile was first transformed into the iminonitrile with use of active carbon at 20°C and then the iminonitrile was hydrogenated over Co–SiO_2 at 114°C and 6.9 MPa H_2 to give **11** in 94.9% yield.[22] In another patent, isophoronenitrile was kept in methanol and ammonia at 40°C for 2.5 h, allowed to cool to room temperature, and then hydrogenated over a supported ruthenium–cobalt catalyst at 120°C and 9.8 MPa H_2 to give 82.1% of the corresponding diamine and cyanoamine.[23]



Scheme 6.5 The products of the reductive amination of menthone (the compounds indicated by asterisks were not found in the products).

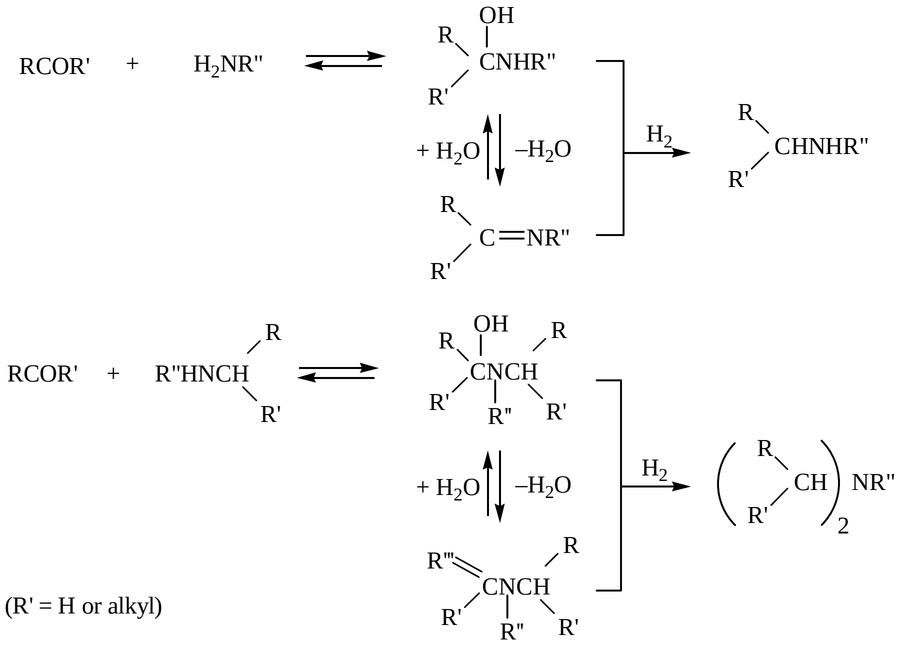


Scheme 6.6 Reductive amination of isophoronenitrile via the formation of an azine.

6.2 REDUCTIVE ALKYLATION OF PRIMARY AMINES WITH CARBONYL COMPOUNDS

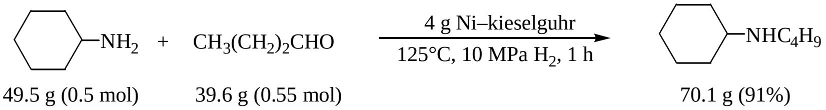
The reaction of a primary amine with a carbonyl compound may give an addition product or an azomethine derived from it, and may give a secondary amine by hydrogenation. If the addition product of the secondary amine with a carbonyl compound has an α-hydrogen adjacent to the carbonyl group, the formation of a tertiary amine may be possible through an enamine as intermediate, although direct removal of the hydroxyl group by hydrogenolysis might also be possible (Scheme 6.7). The reductive alkylation of primary amines with a carbonyl compound provides a useful method for the preparation of mixed secondary amines, RNHR′, which are seldom easy to prepare by other methods.[24] Skita et al. alkylated primary and secondary amines with an aldehyde or ketone using a colloidal platinum mostly in water at room temperature and 0.3 MPa H_2.[12,25] Fair to good yields of secondary amines were obtained from an equimolar mixture of primary amine and carbonyl compound under these conditions. Thus, there have been prepared ethylisoamylamine in good yield from isoamylamine and acetaldehyde, *s*-butylmethylamine in 69% yield from methylamine and ethyl methyl ketone, *N*-isopropylcyclohexylamine in 79% yield from cyclohexylamine and acetone, and *N*-*s*-butylcyclohexylamine in 60% yield from cyclohexylamine and ethyl methyl ketone. However, the reaction of cyclohexylamine and diethyl ketone gave only a 31% yield of *N*-(1-ethylpropyl)cyclohexylamine. It appears that the yield of secondary amines decreases in the cases of the ketones without at least one methyl group.

Winans and Adkins obtained *N*-butylcyclohexylamine (eq. 6.8) and *N*-butylpiperidine in 91 and 93% yields, respectively, by hydrogenating a mixture of cyclohexylamine or piperidine with slightly molar excess of butyraldehyde over Ni–kieselguhr at 125°C and 10 MPa H_2.[26] Under similar conditions hydrogenation of



Scheme 6.7 Reductive alkylation of a primary amine with an aldehyde or ketone to produce secondary and tertiary amines.

an equimolar mixture of cyclohexylamine and cyclohexanone gave dicyclohexylamine in 70% yield, along with 28% of cyclohexanol. Hydrogenation of a mixture of β-phenethylamine and butyraldehyde, however, afforded only a low yield (36%) of *N*-butyl-β-phenethylamine along with 11% of *N,N*-dibutyl-β-phenethylamine and 21% of unreacted β-phenethylamine.



(6.8)

Henze and Humphreys prepared various *N*-alkylbutylamine by hydrogenating the aldimines or ketimines, obtained by adding a hydrocarbon solution of aldehyde or ketone to a hydrocarbon solution of butylamine and drying over anhydrous potassium carbonate or sodium sulfate in the case of aldimines but without isolating the imines, over Raney Ni at 75°C and an initial hydrogen pressure of 21 MPa.[24] Thus *N*-methyl-, *N*-ethyl-, *N*-propyl-, *N*-isopropyl-, *N*-isobutyl-, *N*-*s*-butyl, *N*-pentyl (eq. 6.9), and *N*-isoamylbutylamines were prepared in 26–56% yields. In the case of *N*-methylbutylamine, obtained from methylamine and butyraldehyde, a significant amount of *N*-methyldibutylamine was also formed.

$$CH_3(CH_2)_3CHO + H_2N(CH_2)_3CH_3 \longrightarrow \left[CH_3(CH_2)_3CH{=}NH(CH_2)_3CH_3 \right] \xrightarrow[75^\circ C,\ 21\ MPa\ H_2,\ <3\ h]{10\ g\ Raney\ Ni} CH_3(CH_2)_4NH(CH_2)_3CH_3 \qquad (6.9)$$

43 g (0.5 mol) in 25 ml Skellysolve* — 36.5 g (0.5 mol) in 25 ml Skellysolve* — 51%

* Chilled in salt-ice, the aldehyde solution added slowly to the amine solution, allowed to stand for 1 h, dried over K_2CO_3 after the water is separated.

Campbell et al. prepared unsymmetric secondary aliphatic amines from aliphatic aldehydes and primary amines in overall yields of 33–63% from the primary amine, by hydrogenation of the isolated aldimines over prereduced platinum oxide in ethanol at room temperature and 0.2–0.3 MPa H_2.[27] The hydrogenation was best carried out in absolute ethanol in the presence of a small amount of the starting primary amine to minimize cleavage of the aldimine. An example is seen in eq. 8.2 for the preparation of butylpropylamine. Prereduced platinum oxide was superior to Pd–C in the rates of hydrogenation and the yields of amine. With Raney Ni the calculated amount of hydrogen was taken up rather rapidly, but distillation of the reduction product yielded little or no secondary amine. Other examples where imines were prepared in situ prior to hydrogenation but subjected to hydrogenation without being isolated are seen in eqs. 8.3 and 8.5.

Cope and Hancock alkylated ethanolamine with ketones containing 3–10 carbon atoms over prereduced platinum oxide in ethanol at room temperature and 1–2 atm of hydrogen.[28] Most of the hydrogenations were exothermic and proceeded rapidly without heating in alcohol solution and gave 2-*sec*-alkylaminoethanols in nearly quantitative yields (mostly 92–98%). The hydrogenations were most rapid with methyl ketones except acetophenone. An example is shown in eq. 6.10. The hydrogenations with cyclic ketones, except *l*-menthone, were equally rapid. In the case of diethyl ketone the hydrogenation was slightly slower, but went to completion without heating. With acetophenone, dipropyl ketone, dibutyl ketone, and *l*-menthone the reaction mixtures were heated to 50–60°C, and rather long reaction times (20–30 h) were required for completing hydrogenation. No reduction occurred with diisobutyl ketone under these conditions. The hydrogenations were much slower in acetic acid, and still slower when Pd–C was used.

$$CH_3CO(CH_2)_5CH_3 + H_2NCH_2CH_2OH \xrightarrow[100\ ml\ EtOH;\ RT,\ 0.1\text{–}0.2\ MPa\ H_2,\ 7\ h]{0.5\ g\ Pt\ oxide^*} C_6H_{13}CH(CH_3)NHCH_2CH_2OH \qquad (6.10)$$

166 g (1.3 mol) — 61 g (1 mol) — 96%

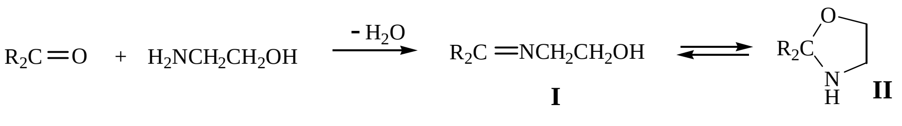
* Prereduced in 50 ml EtOH at 1 atm H_2.

Raney Ni and copper–chromium oxide can be used satisfactorily for these reductive alkylations at elevated temperatures and pressures in ethanol solution or without a solvent (eq. 6.11). 2-*prim*-Alkylaminoethanols were prepared in a similar manner in 60–90% yields by hydrogenating mixtures of aldehydes with ethanolamine. In these cases the alcohol solution of ethanolamine was cooled in ice while the aldehyde (15% molar excess) was added slowly in order to avoid polymerization.

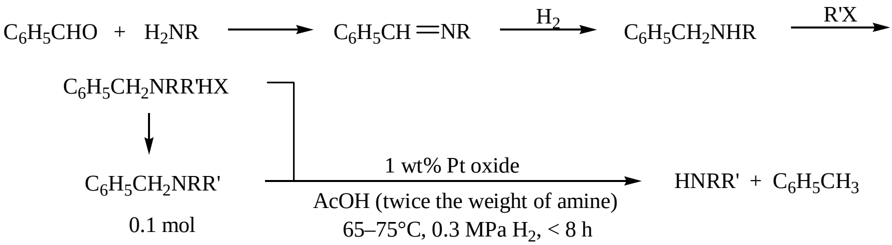
$$\underset{28\text{ g }(0.39\text{ mol})}{CH_3COC_2H_5} + \underset{18\text{ g }(0.3\text{ mol})}{H_2NCH_2CH_2OH} \xrightarrow[\substack{3\text{ g Raney Ni, }150^\circ C \\ 1\text{ g Cu–Cr–Ba oxide, }160^\circ C}]{6.9\text{–}13.8\text{ MPa }H_2} \underset{\substack{27.2\text{ g }(86\%) \\ 28.5\text{ g }(88\%)}}{C_2H_5CH(CH_3)NHCH_2CH_2OH} \quad (6.11)$$

The condensation products of ketones with ethanolamine, the intermediates of the hydrogenations, were found to be not alkylideneaminoethanols (**I**), but oxazolidines (**II**), which were converted to 2-alkylaminoethanols on hydrogenation. In solution, oxazolidines are considered to exist in fairly mobile equilibrium with the corresponding alkylideneaminoethanols (Scheme 6.8). In cases of certain hindered ketones, however, the condensation products may be the alkylideneaminoalcohols. For example, the condensation product obtained from diisobutyl ketone and ethanolamine has been shown to be largely or completely in the form of the alkylideneaminoalcohol. A number of 1-alkylamino-2-propanols,[29] 2-alkylamino-1-propanols,[30] 2-alkylamino-1-butanols,[30] 2-alkylamino-2-methyl-1-propanols,[30] 1-alkylamino-2-methyl-2-propanols,[30] and 3-alkylamino-1-propanols[31] were prepared similarly. Steric hindrance of either the carbonyl or the amino group slowed the reaction. It was necessary to prepare the anhydro compounds before hydrogenation in the cases of diisobutyl ketone with 2-amino-1-propanol and 2-amino-1-butanol. The hydrogenation of ketones with 2-amino-2-methyl-1-propanol in the presence of platinum or Raney Ni failed to give the alkyl derivatives, although the oxazolidines from an aldehyde could be hydrogenated in the presence of platinum. Those from ketones were hydrogenated with Raney Ni at higher temperatures. However, hydrogenations of ketones with 1-amino-2-methyl-2-propanol in which the amino group is not hindered proceeded rapidly and gave high yields of the alkyl derivatives.

Buck and Baltzly have described a method that gives good yields of dialkylamines by the use of reductive debenzylation of benzyldialkylamines.[32] Benzaldehyde is condensed with a primary aliphatic amine to give a Schiff base, which is then catalytically reduced to the corresponding benzylalkylamine. Addition of an alkyl halide (or, in the case of methylamine, reductive methylation) gives the hydrohalide of the benzyldialkylamine. Reductive debenzylation of the hydrohalide or the corresponding base gives dialkylamine and toluene or methylcyclohexane (Scheme 6.9). The Schiff base may be purified (e.g., by distillation), but usually this is unnecessary as any remaining primary amine is eliminated on distilling the benzylalkylamine. Since the benzylalkylamine does not undergo hydrogenolysis, any unchanged benzylalkylamine that was



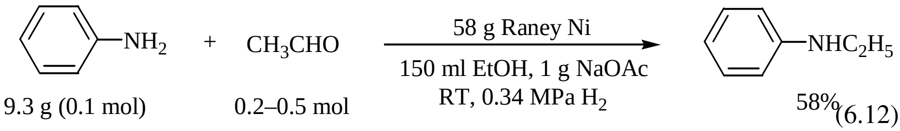
Scheme 6.8 Condensation products of ethanolamine with carbonyl compounds.



Scheme 6.9 Preparation of dialkylamines by reductive debenzylation of benzyldialkylamines.

not separated from the tertiary benzylamine by distillation may be removed after reduction. The benzyldialkylamine, as base or salt, is best hydrogenolyzed over platinum oxide in acetic acid. Pd–C, which retains its activity longer, may be used and Raney Ni may also be used with the free base in ethanol, but the platinum catalyst was superior.

Emerson and Waters alkylated primary aromatic amines with C_2–C_7 aliphatic aldehydes and benzaldehyde over Raney Ni in the presence of sodium acetate as a condensing agent and obtained *N*-alkylanilines in 47–65% yields.[33] With C_2–C_5 aldehydes, up to 10% of the tertiary amines were produced, but no tertiary amines were found in the case of heptanal and benzaldehyde. With acetaldehyde in the absence of sodium acetate , aniline was recovered unchanged over platinum oxide and a mixture of amines resulted over Raney Ni, compared to 41 and 58% yields of *N*-ethylaniline over platinum oxide and Raney Ni (eq. 6.12), respectively, in the presence of sodium acetate.

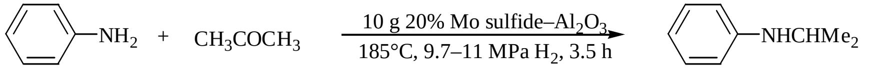


(6.12)

Similarly, *N*-ethyl-1-naphthylamine was prepared in 88% yield, and *N*-ethyl-, *N*-butyl- and *N*-benzyl-2-naphthylamine, and *N*-ethyl- and *N*-butyl-*p*-toluidine were prepared in 50–64% yields.[34] In the alkylation of *p*-toluidine and *p*-anisidine with butyraldehyde, *N,N*-dibutyl derivatives were also produced in 19 and 25% yields, respectively. The Emerson–Waters procedure was also applied to the reductive alkylation of 2-phenylpropylamines and 2-phenylisopropylamines with C_1–C_3 aldehydes (amine : aldehyde ratio = 1 : 3).[35] With higher aldehydes the monosubstituted products were isolated in good yields (in 48–94% yields with acetaldehyde), while with formaldehyde *N,N*-dimethyl derivatives were obtained in 51–85% yields.

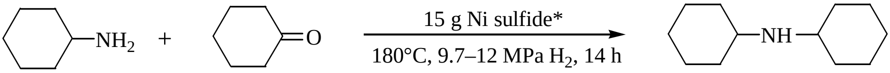
Dovell and Greenfield have shown that base metal sulfides as well as noble metal sulfides are excellent catalysts for the preparation of secondary amines by the reductive alkylation of primary amines (or their nitro precursors) with ketones.[36,37] There was little or no hydrogenation of aromatic rings for arylamines, an important side re-

action over nickel and platinum metal catalysts. The sulfides of rhenium, iron, cobalt, nickel, molybdenum, tungsten, and nickel–tungsten were active catalysts for the reductive alkylation and gave good results with both alkyl- and arylamines. The reductive alkylation of aniline and cyclohexylamine with acetone and cyclohexanone, respectively, are shown in eqs. 6.13 and 6.14.[36]



70 g (0.75 mol) 131 g (2.25 mol) 91% (+ 4% aniline) (GC)

(6.13)

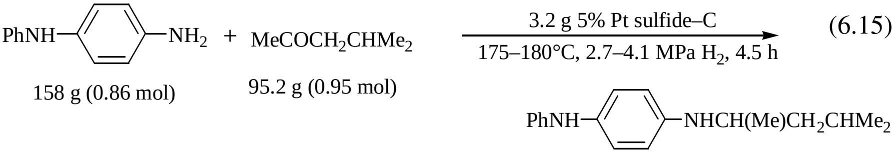


99 g (1.0 mol) 186 g (1.90 mol) 95.5%

* Supported on montmorillonite (15% Ni).

(6.14)

Rhenium sulfide was the most active and hydrogenated excess ketone to the corresponding alcohols. The platinum metal sulfides were found to be more active than the base metal sulfides and highly selective for the formation of *N*-alkylarylamines. They usually produce a pure product with little or no side reactions, require no excess above the stoichiometric amount of ketone, and are active at relatively low pressures of hydrogen. An example with *N*-phenyl-*p*-phenylenediamine is shown in eq. 6.15.[37] Platinum metal sulfides may also be used for the reductive alkylation of aliphatic amines and their nitroalkane precursors with aliphatic ketones.



(6.15)

158 g (0.86 mol) 95.2 g (0.95 mol)

228 g (99%)

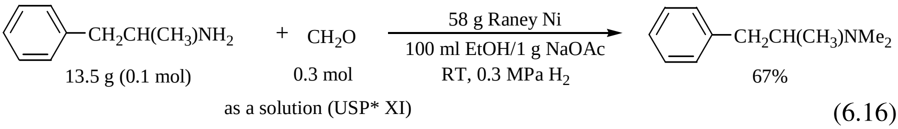
The reductive alkylation with aldehydes to prepare *N*-*n*-alkylarylamines generally leads to a mixture of *N*,*N*-dialkyl- and *N*-alkylarylamines, and the yields of alkylated amines are often poor with aldehydes other than formaldehyde (see eq. 6.12).

6.3 PREPARATION OF TERTIARY AMINES

The preparation of tertiary amines by reductive alkylation of ammonia appears to find only limited application. Triethylamine and tripropylamine were prepared by hydrogenation of acetaldehyde and propionaldehyde, respectively, in the presence of ammonia over platinum catalyst.[38] A high yield (84.1% by GC) of trinonylamine was

obtained by hydrogenating an approximately 2:1 molar mixture of nonanal and ammonia over Pd–C without a solvent at 100°C and 6.9 MPa H_2 (see eq. 6.4). This characteristic tendency of Pd–C to favor the tertiary amine formation is in line with the observation that tertiary amines were formed in high yields in the hydrogenation of aliphatic nitriles over Pd–C, in particular in aqueous ammonia (see Section 7.5).[39]

The reductive alkylation of a primary amine to give tertiary amine is often successful with formaldehyde over nickel catalyst. Thus aralkylamines $ArCH(CH_3)CH_2NH_2$ and $ArCH_2CH(CH_3)NH_2$ were converted to *N,N*-dimethyl derivatives in 51–85% yields with formaldehyde and hydrogen over Raney Ni in ethanol in the presence of sodium acetate (eq. 6.16).[35]



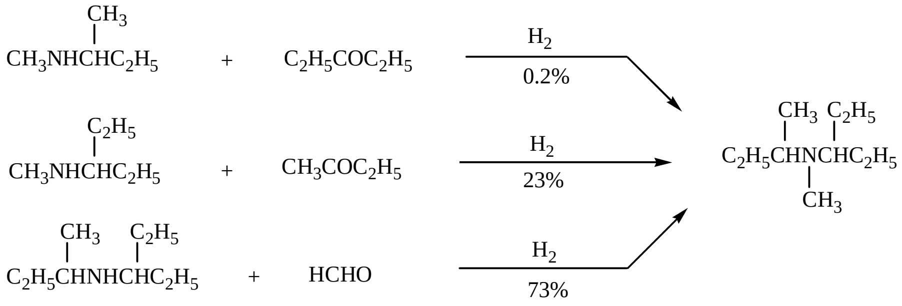
(6.16)

* *United States Pharmacopoeia*

Triethylamine was obtained in a yield of 16% by alkylating ethylamine drop by drop with acetaldehyde in a 1:2 molar ratio in a colloidal platinum solution at room temperature and 0.1 MPa H_2.[12] Benzyldiethylamine was prepared in a 31% yield from ethylamine, benzaldehyde, and acetaldehyde in a 1:1:1 molar mixture over a colloidal platinum in H_2O–AcOH–EtOH at room temperature and 0.3 MPa H_2. The yield of the tertiary amine, however, was improved to more than 50% by alkylating ethylbenzylamine with acetaldehyde.

A more general method for the preparation of tertiary amines is the reductive alkylation of secondary amines with carbonyl compounds. Skita et al. alkylated various secondary amines with a 2 molar ratio of aldehydes and ketones over a colloidal platinum at room temperature and 0.3 MPa H_2.[25] The alkylation with aldehydes was applicable to a wide range of secondary amines, including diphenylamine, whereas the alkylation with ketones depended greatly on the structure of both ketones and amines. Scheme 6.10 is an example showing how the yield of (2-butyl)(3-pentyl)(methyl)amine depends on the structure of starting compounds. In general, the alkylation of secondary amines containing at least one methyl group by methyl ketones with lower alkyl groups gave good results, although the yields were not high (47% at the highest). The results by Skita et al. on the reductive alkylation of various secondary amines with aldehydes and ketones are summarized in Table 6.4.

Malz, Jr. and Greenfield studied the preparation of tertiary amines by reductive alkylation of aliphatic secondary amines with ketones, using platinum metals and their sulfides as catalysts.[40] Excellent yields of tertiary amines were obtained with unhindered ketones, such as cyclohexanone and acetone, and relatively unhindered secondary amines. In this study, 5% Pd–C and various transition metal sulfides were compared in the reductive alkylation of dibutylamine with cyclohexanone. By using the reaction conditions suitable to each catalyst, excellent yields of tertiary amines were obtained, as shown in Table 6.5. Approximately 5–15% of the excess cyclohex-



Scheme 6.10 Preparation of (2-butyl)(3-pentyl)(methyl)amine from three different pairs of compounds.

TABLE 6.4 Reductive Alkylation of Secondary Amines with Aldehydes and Ketones over Platinum Catalyst[a,b]

Secondary Amine Alkylated	Aldehyde or Ketone	Yield of Tertiary Amine (%)
$C_2H_5NH(CH_2)_2CH(CH_3)_2$	$CH_3(CH_2)_5CHO$	19
$C_2H_5NH(CH_2)_2CH(CH_3)_2$	Citral	47
$[(CH_3)_2CH(CH_2)_2]_2NH$	CH_3CHO	34
$[(CH_3)_2CH(CH_2)_2]_2NH$	$CH_3CH{=}CHCHO$	44
$[(CH_3)_2CH]_2NH$	CH_3CH_2CHO	26
$[(C_2H_5CH(CH_3)]_2NH$	$CH_3(CH_2)_5CHO$	5.7
Ph_2NH	HCHO	63
Ph_2NH	CH_3CHO	80
Ph_2NH	CH_3CH_2CHO	53
Ph_2NH	$CH_3(CH_2)_2CHO$	33
Ph_2NH	$(CH_3)_2CHCHO$	7.5
$CH_3NHCH(CH_3)C_2H_5$	CH_3COCH_3	47
$CH_3NHCH(CH_3)C_2H_5$	$CH_3COCH_2CH_3$	18
$CH_3NHCH(CH_3)C_2H_5$	$CH_3CO(CH_2)_2CH_3$	17
$CH_3NHCH(CH_3)C_2H_5$	$CH_3CO(CH_2)_3CH_3$	7.6
$CH_3NHCH(CH_3)C_2H_5$	$CH_3CO(CH_2)_4CH_3$	2.7
$CH_3NHCH(CH_3)C_2H_5$	$CH_3CO(CH_2)_5CH_3$	0.6
$CH_3NHCH(CH_3)C_2H_5$	Cyclohexanone	15
$CH_3NHCH(CH_3)C_2H_5$	4-Methylcyclohexanone	3.8
$CH_3NHCH(CH_3)C_2H_5$	3-Methylcyclohexanone	4.8
$CH_3NHCH(CH_3)C_2H_5$	2-Methylcyclohexanone	0
$C_2H_5NHCH(CH_3)C_2H_5$	CH_3COCH_3	2.1
$C_2H_5NH(CH_2)_2CH(CH_3)_2$	CH_3COCH_3	24
$[(CH_3)_2CH(CH_2)_2]_2NH$	CH_3COCH_3	14

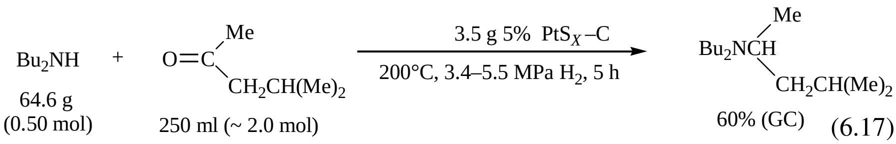
[a]Data of Skita, A.; Keil, F.; Havemann, H. *Ber. Dtsch. Chem. Ges.* **1933**, *66*, 1400.
[b]1:2 molar ratio of amine: carbonyl compound was hydrogenated over colloidal platinum in aqueous solution or suspension at room temperature and 0.3 MPa H_2.

TABLE 6.5 Reductive Alkylation of Dibutylamine with Cyclohexanone[a,b]

					Yield (mol%)	
Catalyst	Amount (g)	T (°C)	H_2 P (MPa)	Time (h)	Tertiary Amine[c]	Cyclohexanol[d]
5% Pd–C	3.5	45–50	2.4–3.4	4.3	98	14
5% Pd–C	3.5	85–95	4.1–5.5	1.4	96	6
5% PtS_X–C	3.5	45–50	3.4–5.5	10.3	84	9
5% PtS_X–C	3.5	105–110	3.4–4.8	0.7	95	—
5% RhS_X–C	3.5	95–100	3.4–5.5	3.8	100	—
PdS_X	—[e]	135–145	3.4–5.5	7.0	94	—
RuS_X	—[f]	75–80	3.4–5.5	3.3	96	—
20% MoS_X–Al_2O_3	7.0	240–250	5.5–6.9	4.3	89	11

[a]Data of Malz, Jr., R. E.; Greenfield, H. in *Heterogeneous Catalysis and Fine Chemicals II*; Guisnet et. al., Eds.; Elsevier Science: Amsterdam, 1991; p 351. Reprinted with permission from Elsevier Science.
[b]Each experiment was run with 64.6 g (0.50 mol) of dibutylamine and 250 ml (~2.4 mol) of cyclohexanone.
[c]*N,N*-Dibutylcyclohexylamine.
[d]Based on excess (1.9 mol) cyclohexanone.
[e]Prepared from 10 g palladium chloride hydrate.
[f]Prepared from 10 g ruthenium chloride hydrate.

anone was hydrogenated to cyclohexanol.The condensation of the ketone was estimated to be about 5% of the excess ketone. Under the same catalyst level and hydrogen pressure, the temperature required for achieving a significant reaction increased from 95°C with acetone, 145°C with ethyl methyl ketone, to 200°C with isobutyl methyl ketone (eq. 6.17).

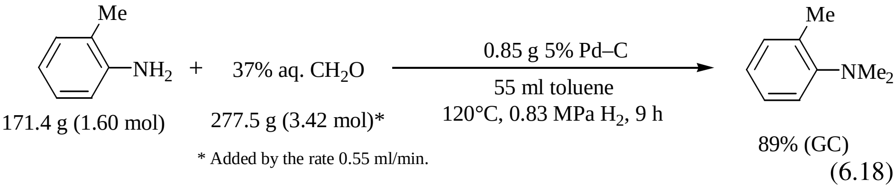


(6.17)

In the reductive alkylation of *N*-ethylcyclohexylamine with cyclohexanone at 160°C and 4.1–5.2 MPa H_2, platinum gave only a 27% conversion of the starting secondary amine and 22% yield of the corresponding tertiary amine, compared with 52% conversion and 42% yield of the tertiary amine with platinum sulfide. Thus, in general, platinum sulfide, or other platinum metal sulfides, have been shown to be the catalysts of choice when more hindered reagents require more severe reaction conditions.

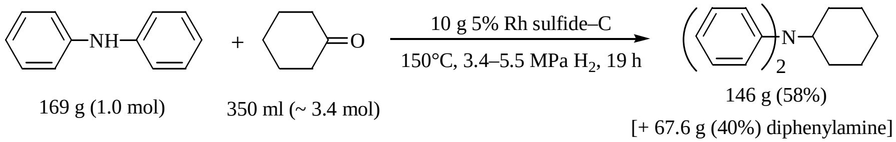
Reductive alkylation of primary arylamines with an aldehyde is often accompanied by side reactions leading to polymeric products, especially with formaldehyde. Gradual addition of an aldehyde to an amine in order to maintain low concentrations of the aldehyde is an effective procedure for minimizing the side reactions.[41] Thus, Bonds and Greenfield obtained high yields of *N,N*-dimethylarylamines by the reductive alkylation of primary arylamines with formaldehyde over Pd–C by gradually adding an

aqueous formaldehyde or using paraformaldehyde.[41] *N,N*-Dimethyl-*o*-toluidine was obtained in an 89% yield (GC) by adding 277.5 g (3.42 mol) of 37% aqueous formaldehyde to 171.4 g (1.60 mol) of *o*-toluidine in 55 ml toluene in a rate of 0.55 ml/min during the hydrogenation over Pd–C at 120°C and 0.83 MPa H_2 (eq. 6.18). *N,N*-Dimethyl-*o*-toluidine was also obtained in 84–85% yields with use of 95% paraformaldehyde, and methanol, 2-propanol, or toluene as a solvent. The alkylation was shown to proceed stepwise through *N*-methyl derivative as the intermediate, which amounted to 60% maximum. The reactivity toward the alkylation decreased in the order with respect to the structure of arylamines: *p*-toluidine >> *m*-toluidine, aniline >> *o*-toluidine as observed by the competitive reaction of aniline with each toluidine.



(6.18)

The reductive alkylation of *N*-alkylarylamines and diarylamine with ketones to give tertiary amines has been investigated by Greenfield and Malz, Jr.[42] with platinum metal sulfides that had been shown to be excellent catalysts for the reductive alkylation of primary arylamines with ketones[37] (see eq. 6.15). Good conversions to tertiary amines were obtained with relatively unhindered secondary arylamines and less hindered ketones. The relative ease in the reductive alkylation of diarylamines with ketones was in the following order: cyclohexanone > acetone > ethyl methyl ketone > isoamyl methyl ketone > isobutyl methyl ketone. For example, 58% of diphenylamine was converted to *N*-alkyldiphenylamine with cyclohexanone over rhodium sulfide at 150°C and 3.4–5.5 MPa H_2 (eq. 6.19), while with isobutyl methyl ketone, a conversion of only 28% was obtained even at 235°C with in the same reaction time.



(6.19)

In a patent, aniline (0.2 mol) was alkylated with acetone (0.82 mol) to give 56% yield of *N,N*-diisopropylaniline over 5% Pd–C (2 g) in acetic acid (140 ml) containing concentrated sulfuric acid (4 ml) at 51°C and 12.4 MPa H_2 for 5 h.[43] *N,N*-Di-*sec*-butylaniline was prepared similarly.

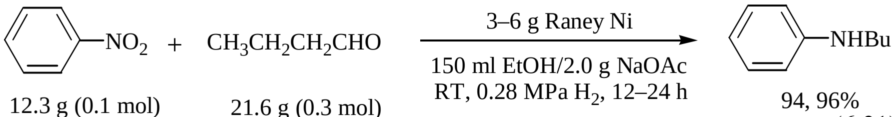
The one-step synthesis of *N,N*-dimethyldodecylamine from dodecanoic acid or its methyl ester, ammonia, methanol, and hydrogen has been studied by Barrault et al. over supported copper–chromium catalysts in a fixed-bed reactor at 300°C and 5 MPa H_2.[44] The selectivity to *N*-methyl- and *N,N*-dimethyldodecylamine was greatly en-

hanced when the catalysts were promoted with Ca or Mn. The total amine selectivity was particularly high (>98%) over Ca-promoted Cu–Cr–Al_2O_3 (eq. 6.20), compared to 80% without promoter.

$$C_{11}H_{23}CO_2Me + NH_3 + MeOH + H_2\ (1:10:40:100) \xrightarrow[\substack{300°C,\ 5\ MPa\ H_2,\ LHSV\ 1/6\ h^{-1} \\ 100\%\ conversion}]{Cu\ (15)\text{–}Cr\ (15)\text{–}Ca_2\text{–}Al_2O_3} \underset{10\%}{C_{12}H_{25}NH_2} + \underset{20.8\%}{C_{12}H_{25}NHMe} + \underset{65.7\%}{C_{12}H_{25}NMe_2} + \underset{3.5\%}{others} \qquad (6.20)$$

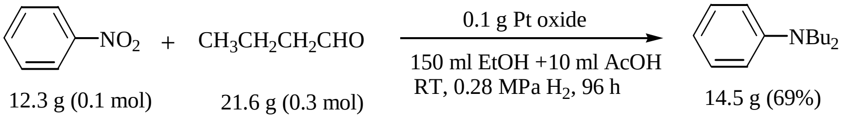
6.4 REDUCTIVE ALKYLATION OF AMINE PRECURSORS

Amine precursors such as nitro and azo compounds may be reductively alkylated with a carbonyl compound. Major hydrogenated *p*-nitrophenol in acetone solution over platinum catalyst and obtained good yields of *p*-hydroxy-*N*-isopropylaniline.[45] Emerson and Mohrman obtained *N*-alkylarylamines from aromatic nitro compounds in 31–96% yields by hydrogenation of an alcoholic solution of the nitro compound and an aldehyde over Raney Ni in the presence of sodium acetate; an example with nitrobenzene and butyraldehyde is shown in eq. 6.21.[46] In the case of *p*-nitrotoluene, appreciable quantities of the tertiary amines (53% of *N,N*-dibutyl-*p*-toluidine with butyraldehyde and 34% of *N,N*-diheptyl-*p*-toluidine with heptanal) were formed. The same procedure was also applied to the preparation of *N*-alkylanilines from azobenzene and aldehydes in 49–74% yield.[47] When an activating group such as hydroxyl or dimethylamino was present in the *ortho* or *para* position, a tertiary amine was produced.

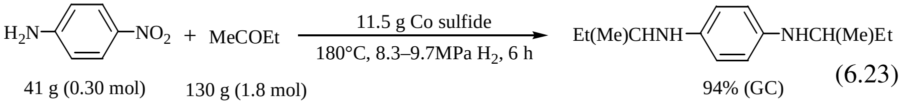


(6.21)

Tertiary arylamines were prepared in good yields by hydrogenation of an alcoholic solution of a nitro compound and an aldehyde over Raney Ni in the presence of triethylamine hydrochloride or, better, over platinum oxide in the presence of acetic acid (eq. 6.22).[48] Base metal and platinum metal sulfides are also effective to the reductive alkylation of nitro compounds with ketones[36,37] as in an example shown in eq. 6.23.

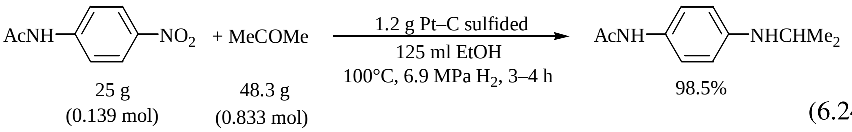


(6.22)



(6.23)

Mylroie et al. studied the optimal conditions for reductive alkylation of *N*-(4-nitrophenyl)acetamide with ketones using Pt–C and sulfided Pt–C.[49] In general, the sulfided catalyst was superior in the yield of the alkylated amines. There was no indication of either reduction of the ketone or saturation of the ring. With a higher loading of ketone (6 equiv) at 100°C and 6.9 MPa H_2 in ethanol, excellent yields (98.5–99%) of the alkylated amines were obtained from the reaction of acetone (eq. 6.24), cyclohexanone, 2-pentanone, and 3-pentanone with *N*-(4-nitrophenyl)acetamide.



(6.24)

6.5 ALKYLATION OF AMINES WITH ALCOHOLS

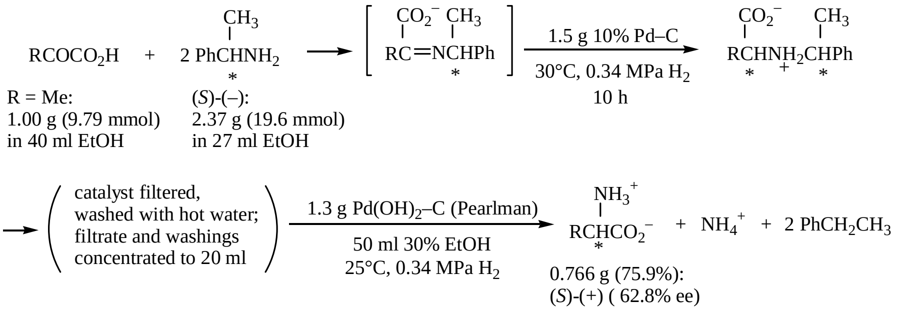
Amines may be alkylated with alcohols at high temperature to give *N*-alkylamines. Adkins and Cramer obtained *N*-ethylcyclohexylamine in an excellent yield by the hydrogenation of aniline in ethanol solution with Ni–kieselguhr as catalyst.[50] When cyclohexylamine (0.55 mol), ethanol (1.2 mol) and Ni–kieselguhr (4 g) were heated at 200°C under 7.5 MPa of hydrogen for 3.5 h, the fraction of the products showed 8.6 g of cyclohexylamine, 42.0 g of *N*-ethylcyclohexylamine, 6 g of *N,N*-diethylcyclohexylamine, and 2.0 g of dicyclohexylamine.[26] Similarly, piperidine and α-methylpiperidine reacted with ethanol, butanol, and cyclohexanol at 200°C to give the corresponding tertiary amines in 76–80% yields. The alkylated amines were obtained in the same yields in an atmosphere of nitrogen as in an atmosphere of hydrogen, although the reaction is believed to involve the dehydrogenation of alcohols to aldehydes or ketones. Reynolds and Greenfield studied a commercial method of preparing *N*-*n*-alkylarylamines in the liquid-phase alkylation of primary arylamines with primary alcohols. The *N*-alkylations can be achieved simply by refluxing a mixture of 5:1 molar ratio of alcohol and arylamine in the presence of Ni–kieselguhr or Raney Ni.[51] The removal of the water formed during the reaction, such as by azeotropic distillation, has been demonstrated to be advantageous for obtaining the alkylarylamines in high yields. As an example, *N*-hexylaniline was obtained in 93% yield by refluxing a mixture of 27.9 g (0.30 mol) of aniline, 153 g (1.5 mol) of 1-hexanol, and 250 ml of toluene in the presence of 5.0 g of Ni–kieselguhr for 5 h at 125°C, with water removed by azeotropic distillation. Good to excellent conversions (47–100%) and yields (43–100% based on converted aniline) of *N*-*n*-alkylanilines were obtained from aniline and ethyl, *n*-propyl, or *n*-hexyl alcohol with the exception of methanol, with which aniline was converted to the product in only <5% yield. None of the catalysts other than nickel (platinum, ruthenium, rhodium, Re–C, and copper–chromium oxide) appeared outstanding or preferable to nickel with the exception of cobalt, although an appreciable amount (7.5% selectivity) of tertiary amine was also formed over this metal. Rusek has found that Pt–Sn–SiO_2 pretreated with Ca^{2+} is useful for the *N*-alkylation of *or-*

tho-disubstituted aniline with both primary and secondary alcohols in the vapor phase at 275°C in the presence of 1 mol H_2/mol aniline.[52]

6.6 SYNTHESIS OF OPTICALLY ACTIVE α-AMINO ACIDS FROM α-OXO ACIDS BY ASYMMETRIC TRANSAMINATION

Hiskey and Northrop prepared optically active α-amino acids by hydrogenating α-oxo acids in the presence of (*R*)-(+)- and (*S*)-(−)-1-phenylethylamine.[53] The reaction was carried out in two steps as described in Scheme 6.11. Thus, a mixture of an α-oxo acid and chiral 1-phenylethylamine in ethanol was first hydrogenated to *N*-(1-phenylethyl)-α-amino acids over 10% Pd–C without isolating the intermediate condensation product (an azomethine). The hydrogenation product was further debenzylated in the presence of Pearlman's palladium hydroxide-on-charcoal catalyst.[54] The debenzylation was not successful with 10% Pd–C (Mozingo), platinum oxide, or Raney Ni, even with the use of various acidic solvents. Since an equivalent of ammonia was produced during the debenzylation, the overall reaction was formulated as shown in the scheme. The failure of the debenzylation with Pd–C catalyst is probably due to a deactivation of the catalyst that may occur when the catalyst containing the surface oxygen is in contact with ethanol.[55] It is probable that such deactivation could be avoided by the use of $Pd(OH)_2$–C catalyst. Nishimura et al. observed that the debenzylation was greatly promoted by a small amount of acetic acid. Acetic acid probably remained in Pearlman's $Pd(OH)_2$–C catalyst since it was finally washed with acetic acid in its preparation.[55] When ethanol is added to a Pd–C catalyst pretreated with hydrogen in cyclohexane, such deactivation can be avoided and the debenzylation reaction may proceed smoothly over an ordinary Pd–C catalyst with addition of a small amount of acetic acid (see Tables 13.6 and 13.7).[55]

The results on the asymmetric transamination of α-oxo acids or ester by Hiskey and Northrop and by Harada and Matsumoto are summarized in Table 6.6.[53,56,57] It is seen that the configuration of the α-amino acid produced is the same as that of the optically



Scheme 6.11 Reductive asymmetric amination of α-oxo acids with chiral 1-phenylethylamine.

TABLE 6.6 Reductive Amination of α-Oxo Acids with Chiral Benzyl- and Naphthylamines[a]

				Amino Acid		
α-Oxo Acid or Ester	Chiral Amine	Catalyst[b]	Yield (%)	ee(%)	Configuration	Ref.
CH_3COCO_2H	(*R*)-(+)-$PhCH(Me)NH_2$	10% Pd–C	47.9	70.6	(*R*) (−)	53
CH_3COCO_2H	(*S*)-(−)-$PhCH(Me)NH_2$	10% Pd–C	43.1	81.5	(*S*) (+)	53
CH_3COCO_2H	(*S*)-(−)-$PhCH(Me)NH_2$	10% Pd–C	78	63	(*S*) (+)	57
$CH_3COCO_2CH_2Ph$	(*S*)-(−)-$PhCH(Me)NH_2$	10% Pd–C	22.0	74	(*S*) (+)	53
CH_3COCO_2H	(*R*)-(+)-1-$C_{10}H_7CH(Me)NH_2$[c]	10% Pd–C	76	80	(*R*) (−)	56
CH_3COCO_2H	(*S*)-(−)-$PhCH(Et)NH_2$	10%Pd-C	76	52	(*S*) (+)	57
$CH_3CH_2COCO_2H$	(*S*)-(−)-$PhCH(Me)NH_2$	10% Pd–C	84.9	62.8	(*S*) (+)	53
$CH_3CH_2COCO_2H$	(*R*)-(+)-$PhCH(Me)NH_2$	$Pd(OH)_2$–C	71.7	43.5	(*R*) (−)	53
$CH_3CH_2COCO_2H$	(*R*)-(+)-$PhCH(Me)NH_2$	PtO_2	59.2	12.6	(*R*) (−)	53
$CH_3CH_2COCO_2H$	(*S*)-(−)-$PhCH(Et)NH_2$	10% Pd–C	69	36	(*S*) (+)	57
$Me_2CHCOCO_2H$	(*R*)-(+)-$PhCH(Me)NH_2$	10% Pd–C	15.7	28.4	(*R*) (−)	53
Me_3CCOCO_2H	(*R*)-(+)-$PhCH(Me)NH_2$	$Pd(OH)_2$–C	0.0	—	—	53
$PhCOCO_2H$	(*R*)-(+)-$PhCH(Me)NH_2$	10% Pd–C	73	29	(*R*) (−)	57
$PhCH_2COCO_2H$	(*R*)-(+)-$PhCH(Me)NH_2$	10% Pd–C	53.8	12.9	(*R*) (+)	53
$PhCH_2COCO_2H$	(*S*)-(−)-$PhCH(Me)NH_2$	10% Pd–C	65.0	12.1	(*S*) (−)	53
$HO_2C(CH_2)_2COCO_2H$	(*S*)-(−)-$PhCH(Me)NH_2$	10% Pd–C	74	13	(*S*) (+)	57

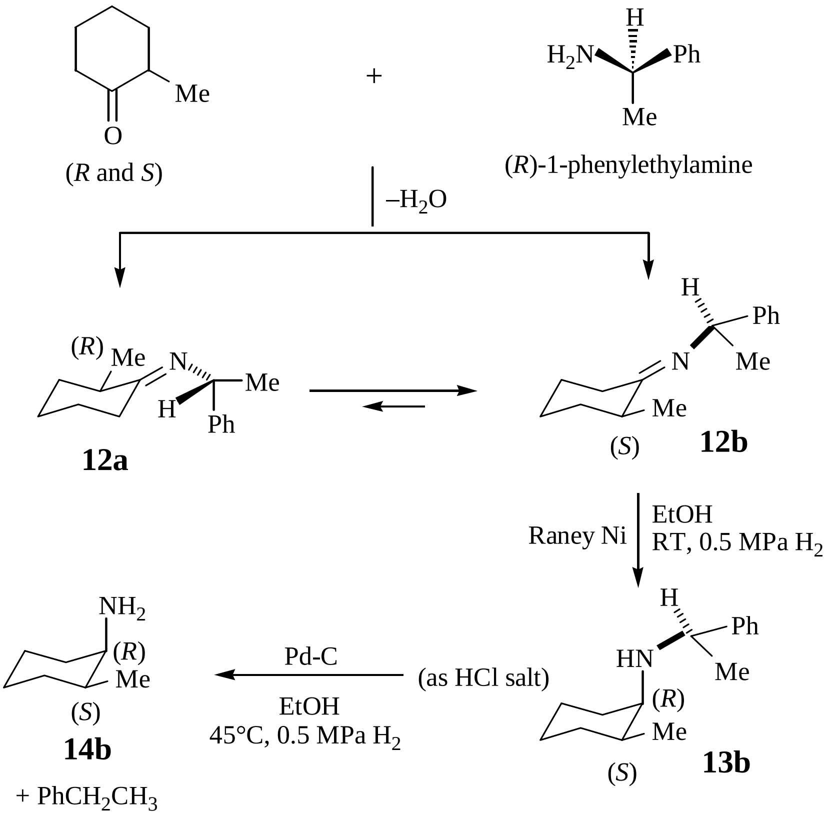
[a]The mixture of α-oxo acid and amine was hydrogenated in ethanol at room temperature and 0.34 or 0.28 MPa H_2.
[b]The catalyst for the hydrogenation of the methine intermediates (Mozingo, R. *Org. Synth., Coll. Vol.* **1955**, *3*, 685). For the debenzylation, $Pd(OH)_2$–C catalyst was used (Hiskey, R. G.; Northrop, R. C. *J. Am. Chem. Soc.* **1961**, *83*, 4798 (see also Pearlman, W. M. *Tetrahedron Lett*. **1967**, 1663).
[c]1-(1-Naphthyl)ethylamine.

active amine from which it is derived. The magnitude of the induced asymmetry depends on the catalyst used and the nature of the alkyl portion of the oxo acids, as well as the structure of the optically active amine. Of the three catalysts used, 10% Pd–C gave a considerably greater % ee as observed in the preparation of butyrine (α-aminobutyric acid). As the size of the alkyl group of the oxo acids increases, the optical purity of the amino acid produced decreases in the order Me > Et > Ph > $PhCH_2$ > $HO_2CCH_2CH_2$. 1-Phenylethylamine induces higher optical purities than 1-phenylpropylamine. Alanine of a high optical purity (80%) was also obtained from pyruvic acid (R = Me) with the use of optically active 1-(1-naphthyl)ethylamine. When benzyl pyruvate was treated with (*S*)-(–)-1-phenylethylamine bimolecular condensation products of pyruvate were formed. The low yield of alanine obtained from the ester (see Table 6.6) may be accounted for by this side reaction.[53]

Harada and Matsumoto studied the effect of solvents on the % ee of the amino acids formed in asymmetric transamination.[56] Generally, the optical activity of alanine prepared from benzyl pyruvate and (*S*)-(–)-1-phenylethylamine decreased with increasing polarity of the solvents used. From the finding that sodium α-phenylglycinate was hydrogenolyzed easily to ammonia and phenylacetate over palladium catalyst, Harada prepared optically active alanine, butyrine, glutamic acid, and aspartic acid in 40–60% optical purities from the corresponding α-oxo acids using α-phenylglycine in aqueous alkaline solution.[58] A solvent effect similar to that observed with 1-phenylethylamine was found with α-phenylglycine esters. In the *trans* amination between ethyl pyruvate and alkyl (*R*)-α-phenylglycinates [$PhCH(NH_2)CO_2R$, R = Me, Et, *i*-Pr], the optical purity of resulting alanine decreased in the order Me > Et > *i*-Pr. The optical purity decreased with increasing polarity of solvent in the order benzene > THF > *t*-BuOH > EtOH > MeOH in cases with the methyl and ethyl esters.[59]

6.7 ASYMMETRIC SYNTHESIS OF 2-SUBSTITUTED CYCLOHEXYLAMINES

Knupp and Frahm obtained optically active 2-substituted cyclohexylamines from racemic 2-substituted cyclohexanones and optically active 1-phenylethylamine according to the three-step procedure outlined in Scheme 6.12 for 2-methylcyclohexanone.[60] The hydrogenation of the imines **12a** and **12b** over Raney Ni proceeds under complete diastereoselective and enantioselective control to give the *cis* secondary amine **13b**. Hydrogenolysis over Pd–C led to highly enantiomerically enriched *cis* primary amine **14b**. These results indicate that the epimeriztion of the diastereomeric imines **12a** and **12b** takes place prior to hydrogenation and that either (1) the diastereomer **12b** is greatly favored at equilibrium or (2) the hydrogenation rate of **13b** is much greater than that of **13a**. Similarly, asymmetric reductive amination has been applied for obtaining optically active, diastereomerically pure 2-substituted cyclopentylamines.[61]



Scheme 6.12 Asymmetric synthesis of 2-methylcyclohexylamine.

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CHAPTER 7

Hydrogenation of Nitriles

7.1 GENERAL ASPECTS

Catalytic hydrogenation of nitriles has long been used for the preparation of various amines. It is performed over metallic catalysts mostly in the liquid phase. The method is also of industrial importance and has been applied to the commercial production of various amines, for example, various aliphatic amines from fatty acid nitriles, hexamethylenediamine (1,6-hexanediamine) from adiponitrile, and xylene-α,α'-diamines [bis(aminomethyl)benzenes] from the corresponding phthalonitriles.

Hydrogenation of nitriles to primary amines (eq. 7.1) is usually accompanied by the formation of secondary amines (eq. 7.2) and even tertiary amines (eq. 7.3). The selectivity to respective amines depends on the structure of substrate, the nature and amount of catalyst, basic and acidic additives, the reaction medium, and other reaction conditions. Among these factors the nature of catalyst appears to be the most important for determining the selectivity.

$$RC{\equiv}N \xrightarrow{2H_2} RCH_2NH_2 \quad + \quad 120\text{ kJ} \tag{7.1}$$

$$2\,RC{\equiv}N \xrightarrow{4H_2} (RCH_2)_2NH \quad + \quad NH_3 \tag{7.2}$$

$$3\,RC{\equiv}N \xrightarrow{6H_2} (RCH_2)_3N \quad + \quad 2\,NH_3 \tag{7.3}$$

The formation of secondary amines probably results from a series of reactions shown in eqs. 7.4–7.6, as originally proposed by von Braun et al. in 1923.[1] The reactions involve the addition of the primary amine produced to the intermediate aldimine **1** to form an α-aminodialkylamine **2** and the Schiff base **3**, which is formed from **2** by loss of ammonia.

$$RC{\equiv}N \xrightarrow{H_2} \underset{\mathbf{1}}{RCH{=}NH} \xrightarrow{H_2} RCH_2NH_2 \tag{7.4}$$

$$RCH{=}NH \;+\; H_2NCH_2R \rightleftharpoons \underset{\mathbf{2}}{RCH(NH_2)NHCH_2R} \xrightarrow{H_2} (RCH_2)_2NH \;+\; NH_3 \tag{7.5}$$

$$\mathbf{2}\ \overset{+NH_3}{\underset{-NH_3}{\rightleftharpoons}}\ \mathbf{3}$$

$$\underset{\mathbf{3}}{RCH{=}NCH_2R} \xrightarrow{H_2} (RCH_2)_2NH \tag{7.6}$$

The formation of tertiary amines is also explained by the analogous reactions shown in eqs. 7.7 and 7.8. In this case, however, elimination of ammonia from the addition product **4** to form an azomethine type compound is not possible, but tertiary amines may be formed either by direct hydrogenolysis of **4** or through the formation of an enamine **5** followed by hydrogenation.

$$\underset{(R'CH_2 = R)}{R'CH_2CH{=}NH} + HN(CH_2R)_2 \rightleftharpoons \underset{\mathbf{4}}{R'CH_2CH(NH_2)N(CH_2R)_2} \xrightarrow{H_2} (RCH_2)_3N + NH_3 \quad (7.7)$$

$$\mathbf{4} \;\underset{+NH_3}{\overset{-NH_3}{\rightleftharpoons}}\; \underset{\mathbf{5}}{R'CH{=}CHN(CH_2R)_2} \xrightarrow{H_2} (RCH_2)_3N \quad (7.8)$$

When the temperature of hydrogenation is high, secondary amine may also be formed from 2 moles of the primary amine produced by loss of ammonia (eq. 7.9).[2–5] Thus, benzylamine was converted to dibenzylamine in more than 90% yield with evolution of ammonia when heated to boiling in xylene (140°C) over Pd–$BaSO_4$ under a stream of hydrogen.[2] In another example, the ratio of primary to secondary amine formed was 1:2.4 when phenylacetonitrile was hydrogenated at 200°C with Ni–kieselguhr as catalyst, compared to 1:0.23 at 125°C,[5] suggesting the occurrence of the reaction 7.9.

$$2\,RCH_2NH_2 \longrightarrow (RCH_2)_2NH + NH_3 \quad (7.9)$$

If the hydrogenation is carried out in an alcohol as solvent, a mixed secondary amine may be formed at high temperature by the reaction of primary amine with the alcohol (eq. 7.10).[6] Over Ni–kieselguhr the reactions shown in eqs. 7.9 and 7.10 become significant at temperatures above 160–170°C.[4]

$$RCH_2NH_2 + R'OH \longrightarrow RCH_2NHR' + H_2O \quad (7.10)$$

The yield of amines from nitriles may be reduced in hydrogenation in the presence of water due to the formation of amides, which results from the addition of water to nitriles (eq. 7.11), although addition of water is often effective in increasing the rate of hydrogenation by depressing the poisoning action of ammonia and thus improving the selectivity to primary amine.[7,8] The effects of water, however, are not so straightforward, as have been discussed in details by Volf and Pasek.[8]

$$RC{\equiv}N + H_2O \longrightarrow RCONH_2 \quad (7.11)$$

The hydration of nitriles to form amides is promoted by metallic catalysts such as nickel and copper,[9] and the copper catalyzed hydration has been utilized in an industrial process for the production of acrylamide from acrylonitrile.[10] The hydration of

nitriles, however, does not appear to occur to any significant extents in the hydrogenation over platinum metals (see, e.g., Table 7.2).

The mechanism for the formation of secondary amine, proposed by von Braun et al., is supported by the fact that the formation of secondary amine decreases with addition of ammonia.[11,12] Ammonia may add to the aldimine **1** competitively with primary amine, forming α,α-diamine **6** (eq. 7.12), and thus may suppress the condensation reaction leading to secondary amine formation (eqs. 7.5 and 7.6). Further, in the presence of ammonia, the intermediates **2** and **3** may be decomposed to give one mole of aldimine and one mole of primary amine by the reversal of the reactions in eqs. 7.5 and 7.6[13,14] and may thus effectively depress the formation of secondary amine.

$$\text{RCH{=}NH} \underset{-\text{NH}_3}{\overset{+\text{NH}_3}{\rightleftharpoons}} \underset{\mathbf{6}}{\text{RCH(NH}_2)\text{NH}_2} \tag{7.12}$$

Mignonac proposed the hypothesis that the formation of dibenzylamine in the hydrogenation of benzonitrile resulted through the intermediate hydrobenzamide **7** formed from benzalimine, as shown in eqs. 7.13–7.15.[15]

$$\text{PhC{\equiv}N} \xrightarrow{\text{H}_2} \text{PhCH{=}NH} \tag{7.13}$$

$$3\ \text{PhCH{=}NH} \longrightarrow \underset{\mathbf{7}}{\text{PhCH(N{=}CHPh)}_2} + \text{NH}_3 \tag{7.14}$$

$$\text{PhCH(N{=}CHPh)}_2 \xrightarrow{3\text{H}_2} \text{PhCH}_2\text{NH}_2 + (\text{PhCH}_2)_2\text{NH} \tag{7.15}$$

A later study by Juday and Adkins with Raney Ni has shown that the behavior of hydrobenzamides toward hydrogenation differs from that of benzonitriles and that the formation of secondary amines through the intermediate hydrobenzamides is not probable.[16]

The mechanism of von Braun et al. is further supported by the formation of mixed secondary and tertiary amines when a nitrile is hydrogenated in the presence of a primary or secondary amine that is different from the one formed from the nitrile. Thus the hydrogenation of phenylacetonitrile in the presence of dipropylamine over a palladium black in alcohol resulted in extensive formation of *N,N*-dipropylphenethylamine,[3] and the hydrogenation of valeronitrile over Raney Ni in the presence of benzylamine and substituted benzylamines led to the formation of corresponding mixed secondary amines.[16]

On the other hand, when *p*-tolunitrile or anisonitrile was hydrogenated in the presence of benzylamine, the secondary products did not contain an appreciable amount of the mixed Schiff base; however, when a mixture of benzonitrile and anisonitrile was hydrogenated, benzal(*p*-methoxybenzyl)amine was formed together

with anisal(p-methoxybenzyl)amine. The failure of mixed Schiff bases to form from the added primary amine during the hydrogenation of aromatic nitriles is not consistent with the mechanism of von Braun et al.; hence, Juday and Adkins suggested the formation of an imine dimer (**8**) for the hydrogenation of aromatic nitriles as a possible intermediate leading to the Schiff base (eq. 7.16) and the secondary amine.[16]

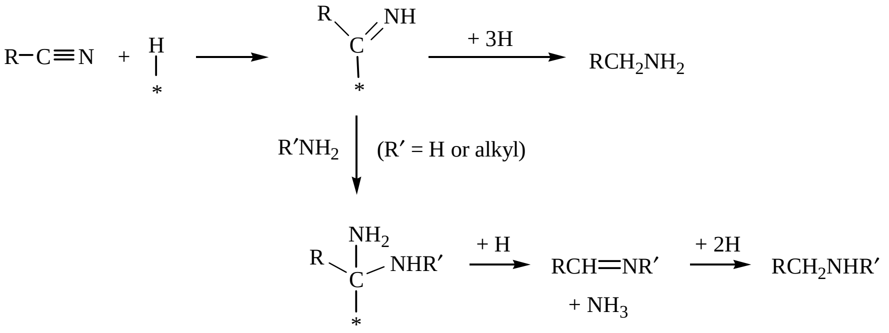
$$2\ ArCH{=}NH \longrightarrow \underset{\mathbf{8}}{ArCH(NH_2)N{=}CHAr} \xrightarrow{H_2} ArCH_2N{=}CHAr \qquad (7.16)$$

Over platinum metal catalysts, however, the hydrogenation of benzonitrile in the presence of butylamine forms benzylbutylamine, the amount of which was greatly dependent on the catalyst and solvent used, although the hydrogenation in the presence of diethylamine afforded no benzyldiethylamine.[17]

Regarding probable courses for secondary and tertiary amine formation, Volf and Pasek take the view that these amines are not formed by direct hydrogenolysis of α-aminodialkylamine **2** and α-aminotrialkylamine **4** (eqs. 7.5 and 7.7), but produced via alkylidenealkylamine **3** and enamine **5** as precursors, respectively (eqs. 7.6 and 7.8).[18] Their view is based on the fact that hydrogenation of valeronitrile in methanol yields large quantities of tripentylamine over Pd–C and Pt–C while hydrogenation of benzonitrile gave no tribenzylamine over Pd–C, Pt–C, and Rh–C, although dibenzylamine was formed extensively over these catalysts (see Table 7.2).[17] In the hydrogenation of benzonitrile, the formation of the enamine intermediate leading to tribenzylamine from α-aminotribenzylamine by loss of ammonia is not possible. The fact that the hydrogenation of benzonitrile over platinum metals in the presence of diethylamine afforded no benzyldiethylamine[17] can be explained for the same reason. Tribenzylamine, however, is formed in the hydrogenation with addition of a large molar ratio of water to benzonitrile over Pt–C (see Table 7.2).[19] In this case, however, it is possible that benzaldehyde, formed by the hydrolysis of the imine **9**, can react with dibenzylamine to form α-hydroxytribenzylamine (**10**), which may be hydrogenolyzed to give tribenzylamine (eq. 7.17).

$$\underset{\mathbf{9}}{PhCH{=}NH} \xrightarrow{H_2O} PhCHO \xrightarrow{(PhCH_2)_2NH} \underset{\mathbf{10}}{PhCH(OH)N(CH_2Ph)_2} \xrightarrow{H_2} (PhCH_2)_3N + H_2O \qquad (7.17)$$

Some mechanistic aspects of the selectivity for the formation of primary and secondary amines have been discussed by Volf and Pasek[20] and Dallons et al.[21] In the hydrogenation of lauronitrile over cobalt catalyst (from decomposition of its formate), the intermediate dodecylidenedodecylamine begins to hydrogenate rapidly only at the



Scheme 7.1 The surface intermediates in hydrogenation of nitriles leading to primary and secondary amines.

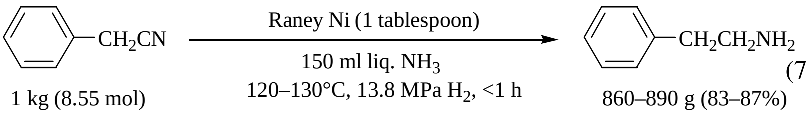
end of the hydrogenation when the nitrile is no longer present. This indicates that on cobalt the adsorption coefficient of the nitrile is substantially greater than that of the intermediate dodecylidenedodecylamine. On the other hand, on nickel the concentration of dodecylidenedodecylamine is lower because of its continuous hydrogenation to didodecylamine. Volf and Pasek conclude that the reason for the difference in selectivity between cobalt and nickel rests on the difference in the relative rates of condensation and hydrogenation on these metals. With pure cobalt as catalyst it has also been found that the selectivity is practically independent of the catalyst concentration in the reaction mixture, suggesting that the condensation reactions leading to secondary amines also proceed on the catalyst surface. A similar view has also been developed by Dallons et al. from their results on the hydrogenation of propionitrile with Raney Ni and supported rhodium catalysts. The selectivity for the formation of propylidenepropylamine and dipropylamine does not increase with the conversion of the nitrile and is nearly constant during hydrogenation. Further, the selectivity for the secondary amine and mixed secondary amine in hydrogenation of a nitrile in the presence of a primary amine different from the one formed from the nitrile is also rather constant with conversion. A great difference in the selectivity for formation of secondary amine has been observed between Rh–C (70%) and Rh–Al_2O_3 (26.8%) in the hydrogenation of propionitrile in methanol at 55°C. From these results, together with the observation that no aldimine is detected in reaction mixtures, Dallons et al. have proposed the view that the selectivity is governed by the two parallel surface reactions, one leading to the primary amine and the other to the secondary amine, which proceed via the surface intermediates shown in Scheme 7.1. The support has been considered to influence the selectivity by adsorbing the primary amine. The alumina support, which is of acidic nature, may adsorb the primary amine strongly and thus depresses the secondary amine formation that occurs on the hydrogenation sites on metal far from the support.

7.2 HYDROGENATION TO PRIMARY AMINES

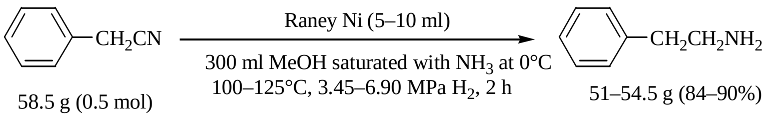
Among various metallic catalysts, nickel and cobalt catalysts have been far more widely used for the hydrogenation of nitriles to primary amines. In general, cobalt catalysts are recognized to be more selective than nickel in the formation of primary amines, although nickel catalysts are usually more active than cobalt catalysts.[22–27] The formation of secondary amine increases with increasing reaction temperature, but the effect of hydrogen pressure is complex and may depend on the nature of catalysts and the structure of nitriles.[28] For minimizing the secondary amine formation with Raney nickel, it has been recommended to carry out the hydrogenation at a temperature and pressure sufficiently high to complete the reaction within a few hours, using a nitrile free of halogen and a relatively high ratio of catalyst.[29] Secondary and tertiary amine formation can be suppressed effectively by hydrogenating nitriles in the presence of ammonia.[11,12] With sterically hindered nitriles, primary amines are formed in higher yields than with unhindered ones. For example, the yields of primary amine were higher with *o*-tolunitrile than with *m*- and *p*-tolunitrile and with α-naphthonitrile than with β-naphthonitrile.[1]

Besson et al. studied the hydrogenation of valeronitrile over Raney Ni, prepared from chromium- and molybdenum-doped Ni_2Al_3 alloys, in cyclohexane at 90°C and 1.6 MPa H_2.[30] Chromium was found to be an effective promoter for initial activity and for the selectivity to primary amine (83–85%, compared to 79.2% with unpromoted catalyst), whereas the addition of molybdenum was not effective.

There are many reports that good yields of primary amines have been obtained over nickel catalysts with addition of ammonia. Minute traces of halide, which are often contained in nitriles owing to their preparative methods, may have a strong poisoning effect on the catalyst, and such impurities should be removed, such as by distilling the nitriles from Raney nickel, before being subjected to hydrogenation. In the hydrogenation of valeronitrile and capronitrile with Raney Ni, Schwoegler and Adkins obtained 90 to 95% yields of primary amines with less than 5% yields of secondary amines, with addition of 2.25–2.29 molar ratios of ammonia to nitrile.[12] Typical hydrogenations in the presence of ammonia are shown in eqs. 7.18[31] and 7.19.[32] Capronitrile, however, was converted to hexylamine in only 67–70% yields under similar conditions.[33]



(7.18)

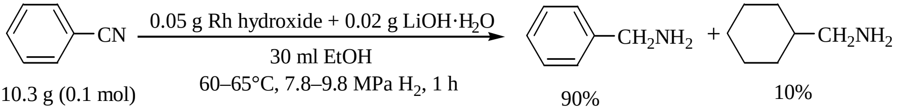


(7.19)

An aliphatic dinitrile sebaconitrile has been converted to 1,10-decanediamine in 79–80% yields with addition of an 8 molar ratio of ammonia to the nitrile (7.20).[34] In this hydrogenation, the presence of ammonia at least in 5 molar ratio to the nitrile was claimed to be necessary to minimize the formation of secondary amine. The hydrogenation of a number of dinitriles, including industrially important adiponitrile and *m*- and *p*-phthalonitriles, has been reviewed by Freidlin and Sladkova.[35]

$$\underset{82\text{ g (0.5 mol)}}{NC(CH_2)_8CN} \xrightarrow[\substack{25\text{ ml EtOH, liq. }NH_3\text{ 68 g (4 mol)}\\125^\circ C,\ 10.3\text{ MPa}H_2,\ 1\text{–}2\text{ h}}]{\text{Raney Ni (6 g in 25 ml 95\% EtOH)}} \underset{68\text{–}69\text{ g (79–80\%)}}{H_2N(CH_2)_{10}NH_2} \quad (7.20)$$

Addition of alkaline substances has also been known to depress secondary amine formation,[7,36–39] although addition of strong alkali such as sodium carbonate and sodium hydroxide may often seriously decrease the rate of hydrogenation.[7,39] The hydrogenation of phenylacetonitrile over Raney Ni gave β-phenethylamine in 92.5% yield with addition of sodium hydroxide at room temperature and atmospheric pressure, whereas with well-washed Raney Ni 51.5% yield of the primary amine and 37.5% yield of the secondary amine were obtained.[36] Likewise, over rhodium catalyst, which is usually highly selective for the formation of secondary amines,[17,19,26,40] benzonitrile was hydrogenated to give benzylamine in 90% yield along with 10% of hexahydrobenzylamine with addition of lithium hydroxide at 60–65°C (eq. 7.21) or with addition of sodium hydroxide at 98–100°C.[39] A similar result has been obtained with a rhodium–platinum oxide of Adams type[41] which is known to be contaminated with alkaline substances resulting from its preparation.[42]



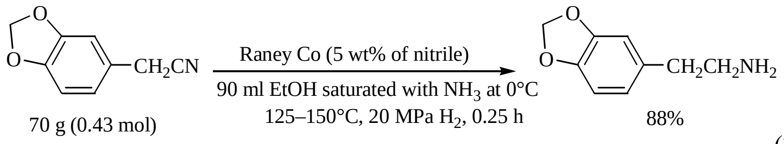
(7.21)

Takagi et al. studied the effects of the nature and amount of added alkalis on the rhodium hydroxide–catalyzed hydrogenation of adiponitrile. The yield of 1,6-hexanediamine increased with increasing amount of added alkali, but the hydrogenation was greatly retarded by the addition of larger amounts of sodium hydroxide. On the other hand, with addition of even larger amounts of lithium hydroxide, the hydrogenation was retarded only slightly and gave an 85% yield of 1,6-hexanediamine (eq. 7.22).[39]

$$\underset{10.8\text{ g (0.1 mol)}}{NC(CH_2)_4CN} \xrightarrow[\substack{30\text{ ml EtOH}\\80^\circ C,\ 7.8\text{–}9.8\text{ MPa }H_2,\ 0.2\text{ h}}]{0.1\text{ g Rh hydroxide + 0.02 g LiOH.}H_2O} \underset{9.86\text{ g (85\%)}}{H_2N(CH_2)_6NH_2} \quad (7.22)$$

There have been many known cases where high yields of primary amines were obtained over cobalt catalysts in the hydrogenation of nitriles. Hydrogenation of 3,4-

methylenedioxyphenylacetonitrile gave homopiperonylamine (3,4-methylenedioxyphenethylamine) in 88% yield with use of Raney Co in ethanol–ammonia (eq. 7.23).[23] It was also noted that Raney Co in dioxane solvent with no ammonia afforded as good results as did Raney Ni even when the latter was used with ethanol–ammonia as the solvent. 4-Chlorobenzonitrile was hydrogenated without dechlorination to give 4-chlorobenzylamine in 91.7% yield over Raney Co in the presence of NH_4Cl in NH_3-saturated methanol at 40°C and 0.88 MPa H_2.[43]

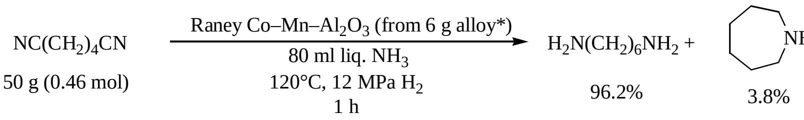


(7.23)

Excellent yields (93–97%) of 1,6-hexanediamine were obtained in the hydrogenation of adiponitrile over Raney Co (eq. 7.24), Co–Al_2O_3 (Raney type), and Co–kieselguhr as catalysts with addition of ammonia.[22] The yields decreased from 97.2 to 93.1% in the absence of ammonia and from 93 to 77% with nickel catalyst in place of cobalt catalyst.

$$\underset{100\text{ g }(0.93\text{ mol})}{NC(CH_2)_4CN} \xrightarrow[\substack{75\text{ g }NH_3\ (4.4\text{ mol})\\ 120°C,\ 6.9\text{–}21\text{ MPa }H_2,\ 0.67\text{ h}}]{\text{Raney Co (8 g as ethanol paste)}} \underset{104\text{ g }(97\%)}{H_2N(CH_2)_6NH_2} \tag{7.24}$$

Taira and Kuroda hydrogenated adiponitrile with Raney Co–Mn–Al_2O_3 catalyst that had been obtained by developing Raney Co–Mn–Al alloy in water with addition of bayerite and a small amount of alkali.[44] The catalyst has been claimed to be highly active and durable for repeated use in the hydrogenation of adiponitrile, affording the product consisting of 96.2% of 1,6-hexanediamine and 3.8% of hexamethylenimine (hexahydroazepine) (eq. 7.25). There are many other patents where this industrially important diamine was obtained in high yields in the hydrogenation over cobalt-based catalysts.[45]



* Co: Mn: Al = 40:5:55.

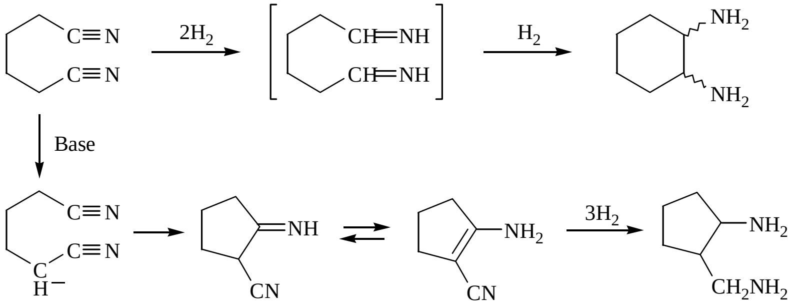
(7.25)

The byproducts of the hydrogenation of adiponitrile are small amounts of hexahydroazepine, 1,2-diaminocyclohexane and 2-(aminomethyl)cyclopentylamine, besides acyclic secondary products. In an example of a continuous process, a 1:12.5 molar ratio of adiponitrile and ammonia that was mixed with 10-fold amount of a hydrogenated reaction mixture from a prior run to give a 1:44 adiponitrile-ammonia mixture

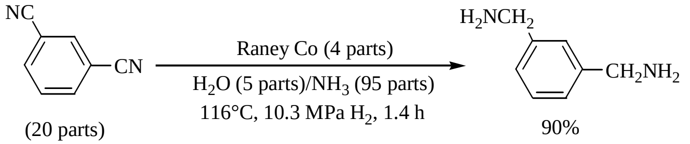
was passed continuously over a 91:5:4 Co–Mn–H_3PO_4 catalyst at 50–95°C and 20 MPa H_2 to give 1,6-hexanediamine contaminated with 0.07% of hexahydroazepine and 1.05% of an acyclic secondary product.[45c] The hydrogenation with iron-based catalysts has also been described in many patents to be useful for obtaining high yields of 1,6-hexanediamine from adiponitrile.[46] In one patent the hydrogenation of adiponitrile over activated Fe_2O_3 in the presence of ammonia at 118–185°C and 32.9 MPa H_2 gave 98.6% of 1,6-hexanediamine and 0.21% of 1,2-diaminocyclohexane.[46c]

Marion et al. discussed the formation pathways of cyclic byproducts in the hydrogenation of dinitriles over Raney Ni.[47,48] 1,2-Diaminocyclohexane has been shown to be formed in a parallel pathway with the hydrogenation of adiponitrile to aminocapronitrile and not in the course of the hydrogenation of the aminonitrile to 1,6-hexanediamine. It has been suggested that the diimino compound is an intermediate leading to the diaminocyclohexane, as shown in Scheme 7.2. The formation of the diaminocyclohexane may be depressed by the addition of sodium carboxylates without any loss of catalytic activity. The formation of 2-aminomethylcyclopentylamine has been considered to take place through the nucleophilic addition of the carbanion formed at the α-carbon to the first electron-withdrawing group in the presence of base to the second electrophilic center to give a Thorpe–Ziegler adduct (see Scheme 7.2). This pathway has been supported by the stereochemistry to give *trans*-aminomethylcyclopentylamine as the major isomer, while the aminomethylcyclopentylamine formed from aminocapronitrile, probably through dehydrogenation to the imino nitrile, affords the *cis* isomer predominantly.

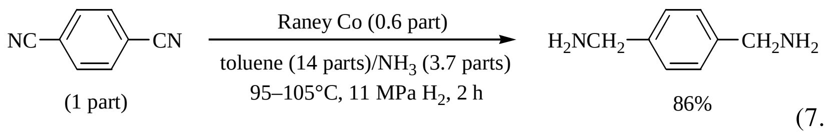
Aromatic dinitriles such as isophthalonitrile and terephthalonitrile were also hydrogenated over Raney Co in the presence of ammonia to give high yields of the corresponding diamines[49–52] (eqs. 7.26[49] and 7.27[50]). Hydrogenation of *o*-phthalonitrile,



Scheme 7.2 The formation pathways of the carbocyclic byproducts in the hydrogenation of adiponitrile.



(7.26)



(7.27)

however, leads to extensive intramolecular cyclization to form isoindoline (see eq. 7.59), and only 9% of the corresponding diamine was obtained under the conditions in eq. 7.26.

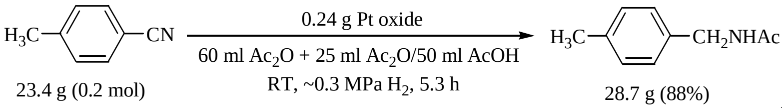
Volf and Pasek compared various cobalt and nickel catalysts in the hydrogenation of stearonitrile at 150°C and 6 MPa H_2.[27] A cobalt catalyst promoted by Mn (5% Mn) gave the best yield of 95.4% of primary amine together with 4.6% of the secondary amine (eq. 7.28). It is to be noted that the high yield was obtained in the absence of ammonia over this catalyst.

$$\underset{80\text{ g }(0.32\text{ mol})}{CH_3(CH_2)_{16}CN} \xrightarrow[150°\text{C, 6 MPa } H_2,\ 0.38\text{ h}]{3\text{ g Co–Mn }(5\%\text{ Mn})} \underset{95.4\%}{CH_3(CH_2)_{17}NH_2} + \underset{4.6\%}{[CH_3(CH_2)_{17}]_2NH} \quad (7.28)$$

High yields of primary amines have also been obtained over cobalt boride as catalyst,[26,53,54] which has been found to be not only highly selective but also less inhibited by solvent and ammonia than other cobalt and nickel catalysts in hydrogenation of nitriles.[26] The hydrogenation of propionitrile in isopropyl alcohol over cobalt boride (5% on C) in the presence of 15:1 molar ratio of ammonia to the nitrile gave propylamine in a high yield of 99% (eq. 7.29).

$$\underset{13.8\text{ g }(0.25\text{ mol})}{CH_3CH_2CN} \xrightarrow[\substack{300\text{ ml } i\text{-PrOH–}NH_3\ (NH_3\text{:nitrile 15:1})\\ 70°\text{C, 0.2 MPa } H_2,\ 26\text{ h}}]{1\text{ g Co boride }(5\%\text{ on C})} \underset{99\%}{CH_3CH_2CH_2NH_2} \quad (7.29)$$

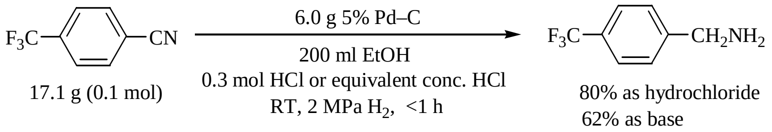
Hydrogenation of nitriles in an acylating solvent or in strongly acidic media has been shown to be effective for preventing the formation of secondary and tertiary amines. The primary amines formed in the hydrogenation of nitriles are acylated in acylating solvents or protonated to form their salts in acidic medium, and thus addition of the amines to the intermediate imines, which may lead to secondary amine formation, is inhibited. Equation 7.30 shows an example of the hydrogenation with an aromatic nitrile carried out in acetic anhydride over Adams platinum oxide as catalyst.[55] This method has been applied to a nickel-catalyzed hydrogenation with addition of sodium acetate or sodium hydroxide (eq. 7.31).[56]



(7.30)

$$\underset{19.5\text{ g }(0.10\text{ mol})}{CH_3(CH_2)_{11}CN} \xrightarrow[\substack{12.0\text{ g NaOAc} + 120\text{ ml } Ac_2O \\ 50°C,\ 0.34\text{ MPa } H_2,\ 1\text{ h}}]{\text{Raney Ni (2–3 g)}} \underset{24.1\text{ g }(100\%)}{CH_3(CH_2)_{12}NHAc} \quad (7.31)$$

Hydrogenation of nitriles in acidic media over palladium or platinum catalysts is also effective to obtain high yields of primary amines. Benzonitrile was hydrogenated to benzylamine in an 80% yield (isolated as hydrochloride) over Pd–$BaSO_4$ in acetic acid in the absence of a mineral acid, although with *p*-hydroxybenzonitrile the secondary amine was the major product.[57] In the case of phenylacetonitrile, addition of dry HCl or concentrated H_2SO_4 was required to obtain a satisfactory yield (73%) of β-phenethylamine. Benzonitrile was also hydrogenated to pure benzylamine hydrochloride very smoothly over Pd–C in absolute ethanol in the presence of ≥1 equiv of hydrogen chloride.[58] Without hydrogen chloride, a mixture of benzylamine, dibenzylamine, and ammonia was obtained. It is of interest that, in the presence of diethylamine, the hydrogenation of benzonitrile with Pd–C in octane, ethanol, or benzene afforded no dibenzylamine, or diethylbenzylamine, but benzylamine quantitatively.[17] The hydrogenation of nitriles in acidic media was also performed with Adams platinum oxide as catalyst.[59–61] Typical hydrogenations in acidic media with palladium[62,63] and platinum catalysts[60,61] are shown in eqs. 7.32–7.35. These procedures, however, were not successful in the hydrogenation of some basic heterocyclic nitriles



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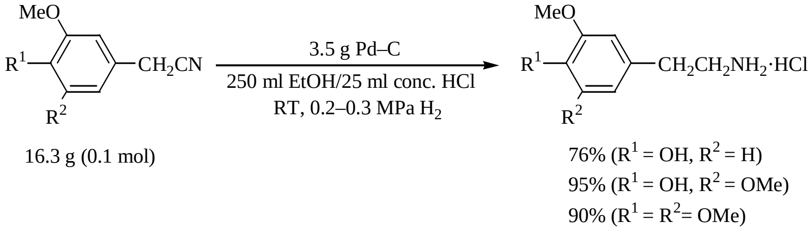

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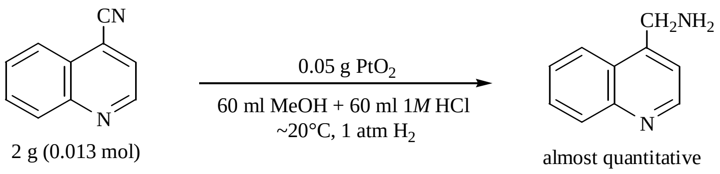


(7.34)

$$\underset{30\text{ g }(0.27\text{ mol})}{NCCH_2CO_2Et} \xrightarrow[\substack{400\text{ ml AcOH}/10\text{ ml conc. }H_2SO_4 \\ 22°C,\ 4\text{ MPa }H_2,\ <1\text{ h}}]{3\text{ g Pt oxide}} \underset{23\text{ g }(74\%)}{H_2NCH_2CH_2CO_2Et} \qquad (7.35)$$

where the formation of difficultly soluble products decreased the rates of hydrogenation and the formation of secondary amines increased.[64] For these basic nitriles, hydrogenation with Raney Ni at room temperature in methanol with addition of 3–4 mol of ammonia for 1 mol of nitrile gave high yields of primary amines (see also eq. 7.51).

7.3 HYDROGENATION OF DINITRILES TO AMINONITRILES

Aminonitriles are often produced in good yields in the hydrogenation of the corresponding dinitriles under controlled conditions. The selective hydrogenation of adiponitrile gives good yields of 6-aminocapronitrile, an intermediate leading to ε-caprolactam for the production of nylon-6. The hydrogenation was studied with a nickel catalyst in EtOH–NH_3 or in the presence of other bases by interrupting the reaction at the uptake of 2 mol of hydrogen.[65] As an example, 1710 g of adiponitrile was hydrogenated over Raney Ni in the presence of 574.4 g of 1,6-hexanediamine and 0.63 g of KOH at 50°C and 2 MPa H_2 to give an 81% conversion and a 60.3% yield of 6-aminocapronitrile, which was converted to ε-caprolactam in more than 98% yield by treating an aqueous solution of the aminonitrile with SiO_2–Al_2O_3.[65c] The hydrogenation was also studied over nickel boride catalysts; 50–60% of 6-aminocapronitrile and 2–5% of 1,6-hexanediamine were obtained. The best results were obtained in the hydrogenation over the catalyst promoted with chromium at 75–80°C and 10 MPa H_2.[66] Ziemecki studied the selective hydrogenation of dinitriles containing 4–12 carbon atoms over Raney Ni at temperatures from 40 to 120°C and hydrogen pressures from 1.5 to 10 MPa.[67] High selectivities to aminonitriles were obtained with dinitriles containing 5–12 carbon atoms over Raney Ni promoted with chromium and iron or with molybdenum in the presence of 10-fold molar excess of MeOH containing 1.5% NaOH or in liquid ammonia. Yields of aminonitriles decreased with increasing temperatures. From the practical point of view, operation of the selective hydrogenations in the range of 50–80°C has been recommended. Selectivity to the corresponding aminonitriles is highest for 5- and 6-carbon systems and lowest for 10- and 12-carbon systems. With glutaronitrile (C_5), up to 15% of aminonitrile was found in the form of dimers; with succinonitrile (C_4), more than 50% of aminonitrile existed as dimers. In a typical run with adiponitrile at 70°C and 3.4 MPa H_2, the concentration of ω-aminocapronitrile in the reaction mixture reached maximum of 72% at ~90% conversion of the dinitrile in the presence of 5 mol of ammonia per mol of dinitrile. It has been suggested that a cyclic intramolecular interaction between the amino group and the cyano group to form a cyclic conformation which is assisted by the presence of NaOH in methanol or in liquid ammonia is responsible for the high selectivity to aminonitriles with C_5 and C_6 dinitriles. In one patent, succinonitrile was converted into a product consisting 96 mol% of aminobutyronitrile and 4 mol% of diaminobutane at 40% conversion in hydrogenation over a prereduced Ni–ZSM-

34 catalyst in diaminoethane at 100°C and 7 MPa H_2.[68] In another patent, succinonitrile was hydrogenated to a product mixture comprising 85% aminobutyronitrile, 14% diaminolactone, and 1% pyrrolidine at 100% conversion over Raney Ni in diaminoethane at 80°C and 7 MPa H_2. The Raney Ni was washed with anhydrous MeOH, treated with KOMe in MeOH and then washed with diaminoethane.[69] Iron catalysts have also been applied to the selective hydrogenation of aliphatic dinitriles to aminonitriles.[70]

Mares et al. studied in details the hydrogenation of α,ω-dinitriles $NC(CH_2)_nCN$ (n = 2–5) to the corresponding aminonitriles over rhodium catalysts (Table 7.1).[71] Highly dispersed rhodium supported on a high-surface-area magnesia has been found to be very selective and efficient to the selective hydrogenation. The selectivities to ω-aminonitriles decreased with increasing chain length between the two cyano groups. Striking differences in the amount and type of byproducts were observed between the dinitriles. In the case of succinonitrile (n = 2) and glutaronitrile (n = 3), the corresponding α,ω-diamines were not formed even at 90% conversion. A cyclic imine was also not found among the products from succinonitrile, and the only byproduct was a dimeric intermediate, $NC(CH_2)_2CH{=}N(CH_2)_3CN$. On the other hand, the only byproduct in the case of 1,5-dicyanopentane (n = 5) was the corresponding diamine. With adiponitrile the selectivity to 6-aminocapronitrile is favored by high dilution, neat ammonia as the reaction medium, and higher hydrogen pressure. Under the best conditions a selectivity of 94% was obtained at 70% adiponitrile conversion (eq. 7.36).

$$NC(CH_2)_4CN \xrightarrow[\substack{NH_3\ (NH_3/AN\ \text{molar ratio} = 12) \\ 100°C,\ 10.3\ MPa\ H_2}]{\text{Rh-MgO (4–5\% Rh, AN/Rh molar ratio = 1340)}} \underset{\substack{94.1\%\ \text{selectivity} \\ \text{at } 70\%\ \text{conversion}}}{H_2N(CH_2)_5CN} \qquad (7.36)$$

AN: adiponitrile

1,4-Cyclohexanedicarbonitrile was converted to a mixture of 61.9% of 4-(aminomethyl)cyclohexanecarbonitrile, 19.8% of 1,4-cyclohexanebis(methylamine), and

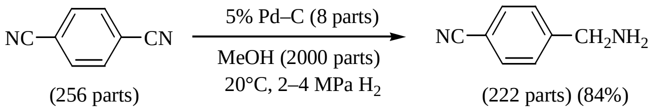
TABLE 7.1 Hydrogenation of α ω -Dinitriles to ω-Aminonitriles over Rh–MgO Catalyst[a,b]

n		Selectivity (%)			
In $NC(CH_2)_nCN$	Conversion (%)	Aminonitrile	Cyclic Imine	Diamine	Dimeric product
2	89.4	87.3	0	0	13.3
3	92.0	81.6	4.1	0.2	12.9
4	90.0	74.0	2.0	21.0	3.0
5	92.7	65.4	0	34.0	0

[a]Data of Mares, F.; Galle, J. E.; Diamond, S. E.; Regina, F. J. *J. Catal.* **1988**, *112*, 145. Reprinted with permission from Academic Press Inc.

[b]Hydrogenations in THF at 100°C and 5.2 MPa H_2 with 21% (w/v) of dinitrile; NH_3/dinitrile molar ratio = 13 and dinitrile/Rh molar ratio = 300.

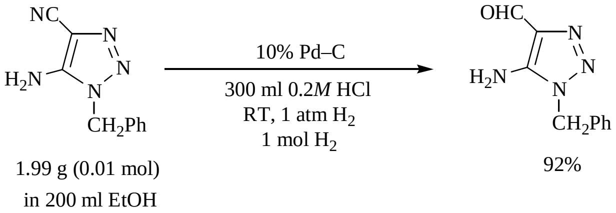
6.3% of 3-azabicyclo[3.2.2]nonane in hydrogenation over Raney Co in dioxane with or without ammonia at 125°C and 10 MPa H_2.[72] With Raney Ni, however, a mixture of 25% of the aminonitrile and 70% of the diamine was obtained. On the other hand, both isophthalonitrile and terephthalonitrile have been converted to the corresponding cyanobenzylamines in high yields in the hydrogenation over palladium catalysts. In a patent, 4-cyanobenzylamine was obtained in 97% yield when 100 parts of terephthalonitrile was hydrogenated in portions over 10 parts of 5% Pd–Al_2O_3 in cumene-ethanol-ammonia at 0–150°C.[73] Likewise, 3-cyanobenzylamine was obtained in 85% yield from isophthalonitrile. Terephthalonitrile was also hydrogenated to give an 84% yield of 4-cyanobenzylamine with Pd–C in methanol at 50% of the hydrogen uptake required for complete hydrogenation (eq. 7.37).[74]



(7.37)

7.4 HYDROGENATION TO ALDIMINES OR ALDEHYDES

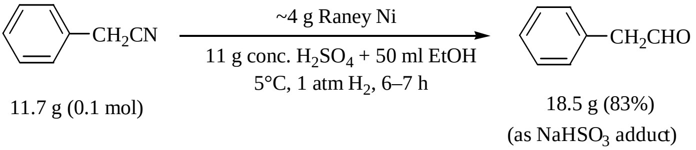
The hydrogenation of nitriles to aldimines or the corresponding aldehydes,[75] formed by hydrolysis of the aldimines, is usually possible under carefully controlled conditions or in those cases where further hydrogenations of the imines or the aldehydes are inhibited by reaction with other functional groups or reagents. Although the formation of an aldehyde has been recognized to an extent of 50% in hydrogenation of an aromatic nitrile,[76] hydrogenation of butyronitrile over Raney Ni in dilute acetic acid gave only a 30% yield of butyraldehyde even when the hydrogenation had been interrupted at the uptake of 1 mol of hydrogen. In the case of phenylacetonitrile the products were a mixture of primary and secondary amines and the starting nitrile only.[77] However, some cases are known where hydrogenation of nitriles over palladium catalyst in the presence of water and mineral acid gives high yields of the corresponding aldimines or aldehydes (eq. 7.38).[78,79]



(7.38)

Hydrogenation of nitriles over Raney Ni in the presence of sulfuric acid has been found more generally applicable for obtaining aldehydes in high yields.[80] In the presence of nitriles Raney Ni is not dissolved into solution with sulfuric acid and retains the activity to hydrogenate nitriles. Thus, the hydrogenation of phenylacetonitrile in H_2SO_4–EtOH over Raney Ni at 5°C and 1 atm gave an 83% yield of phenylactaldehyde, which was isolated as the hydrogen sulfite adduct (eq. 7.39).[75] This method is

especially useful for the synthesis of α-hydroxy aldehydes from the corresponding cyanohydrins. An example with mandelonitrile is shown in eq. 7.40.[81]



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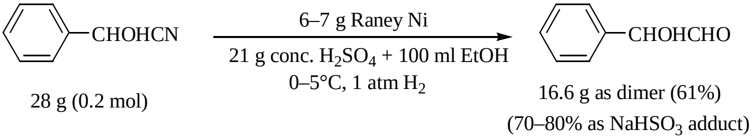
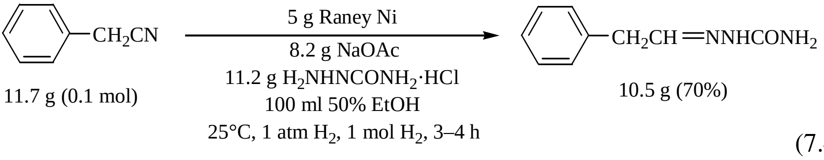


(7.40)

Hydrogenation of nitriles in the presence of carbonyl reagents may give the corresponding aldehyde derivatives in high yields. The aldehydes are readily recovered by hydrolysis of the products. According to Plieninger and Werst, in the hydrogenation of aliphatic and arylaliphatic nitriles with Raney Ni, use of semicarbazide gives better results than other reagents such as phenylhydrazine, toluenesulfohydrazide, benzhydrazide, hydroxylamine and hydrogen sulfite.[77] Hydrogenation at atmospheric pressure gives better results than at elevated pressures. Raney Ni gives better yields than Raney Co. The hydrogenation of phenylacetonitrile (eq. 7.41) and indolyl-3-acetonitrile gave especially good yields of the semicarbazones of the corresponding aldehydes (70 and 75%, respectively). Indolyl-3-acetonitrile was also hydrogenated in the presence of 1,2-dianilinoethane to form a tetrahydroimidazole derivative that was easily hydrolyzed at 20°C with 19% hydrochloric acid to give indolyl-3-acetaldehyde (eq. 7.42).



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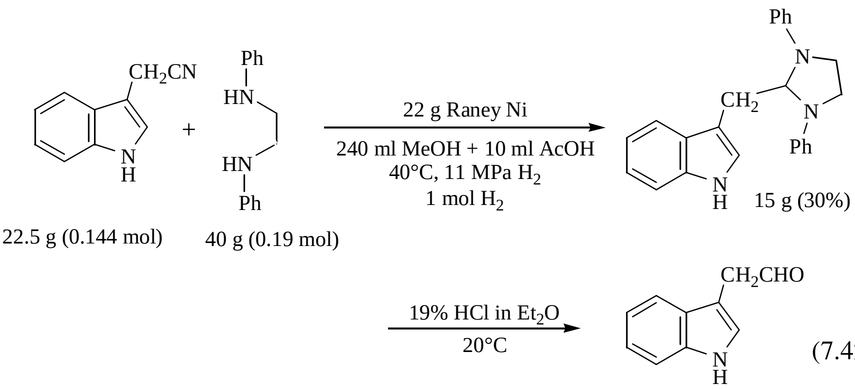
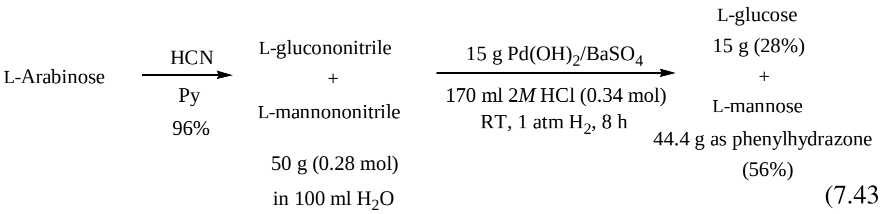
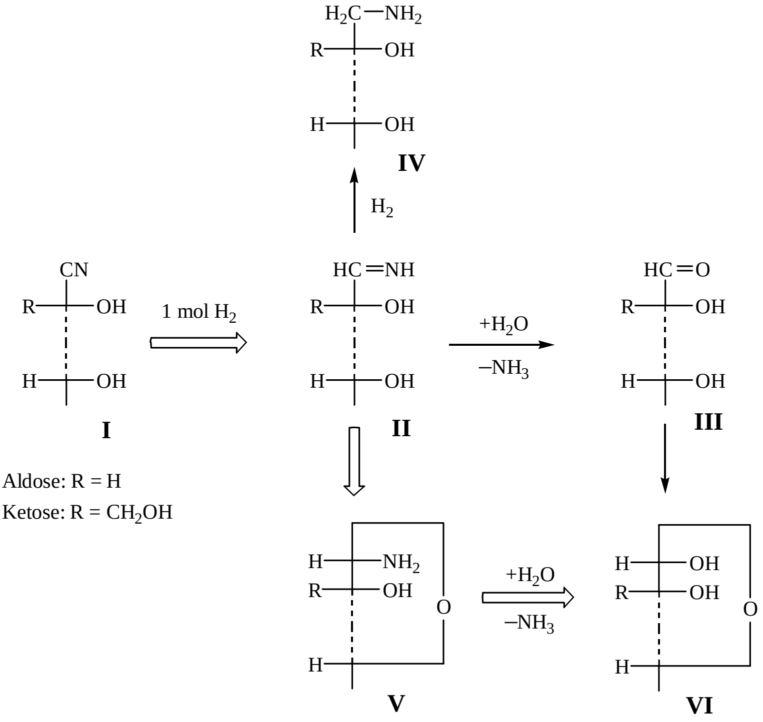


(7.42)

In the hydrogenation of γ- and δ-hydroxynitriles the intermediate aldimines may react with the hydroxyl group to form aminotetrahydrofurans or -pyrans, which protect the aldimines from further hydrogenation to amines. This method has been used by Kuhn and co-workers to lengthen the carbon chain of aldoses and ketoses by hydrogenating their cyanohydrins with palladium catalyst.[82–84] Thus, the hydrogenation of a mixture of L-gluconic acid and L-mannonic acid nitriles, obtained from L-arabinose, over Pd–$BaSO_4$ in dilute hydrochloric acid solution gave 28% of L-glucose and 56% of mannose phenylhydrazone (eq. 7.43).[83]



(7.43)



Scheme 7.3 The reaction routes for the synthesis of aldoses with one more carbon chain involving the hydrogenation of the cyanohydrins.

Both D- and L-arabinose cyanohydrin have been transformed to the amino, arylamino, and benzylaminonitriles, which, on hydrogenation followed by hydrolysis, gave D- and L-glucosamine hydrochloride in 70–75% yields.[82] Fructose cyanohydrin, which is less stable than the cyanohydrin of an aldose, has been hydrogenated to give α-D-fructoheptose in 61% yield (as an acetal with acetone).[84] General reaction pathways of these transformations are formulated in Scheme 7.3. The aldimine **II** formed from the cyanohydrin **I** is cyclized to give glycosylamine **V** much faster than the hydrolysis of **II** to form the aldehyde **III** or the hydrogenation to form the amine **IV**. Thus the aldose **VI** is formed from the cyanohydrin **I** by the reaction pathway **I** → **II** → **V** → **VI**.[84]

7.5 HYDROGENATION TO SECONDARY AND TERTIARY AMINES

Hydrogenation of aliphatic nitriles over platinum metal catalysts often results in extensive formation of secondary and tertiary amines.[7,17,26,85] For example, hydrogenation of butyronitrile over Rh–C in water at 100–125°C and 2.76–4.14 MPa H_2 gave a mixture of 51.5% of butylamine and 48.5% of dibutylamine, while in hydrogenation with addition of ammonia (167 mol% based on butyronitrile) dibutylamine was formed quantitatively. Under similar conditions the hydrogenations with Pd–C and Pt–C gave tributylamine in yields exceeding 95%.[7]

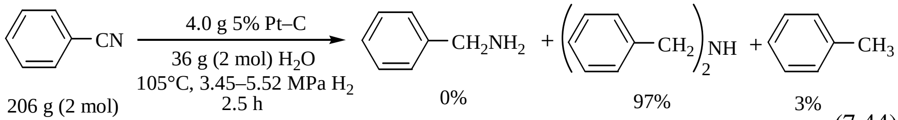
Hydrogenations in methanol tend to be poisoned by ammonia. It is noteworthy that, in contrast to the hydrogenation with nickel and cobalt catalysts, the yields of secondary and tertiary amines even increased in the presence of ammonia over these platinum metal catalysts.

The hydrogenation of aliphatic nitriles over the catalysts based on copper also gives high yields (70–90%) of secondary amines.[86] In a patent, high yields of secondary amines were obtained in a two-stage process in the hydrogenation of fatty nitriles over nickel catalyst.[87] In the first stage, fatty nitriles, such as C_{12} nitrile, is hydrogenated to primary and secondary amines at 120–220°C and 1.5–3.3 MPa H_2, and in the second stage the primary amines are transformed (deaminated) into secondary amines at 150–200°C and 0–1.0 MPa H_2. Product mixtures typically contain 91–94% secondary amines. In another patent, a high yield (93.2%) of secondary amine was obtained by hydrogenation of tallow nitrile (a mixture of C_{18} and C_{16} nitrile) over a Ni–Cu–Cr–Mo catalyst at 155°C and 3.4 MPa H_2 in cyclohexane in the presence of ammonia.[88] Removing of NH_3 in the course of the transformation of primary to secondary amines may improve the yield of secondary amine.[89]

Hydrogenation of aromatic nitriles over platinum metals gives the results on product distribution that are, in certain respects, different from those with aliphatic nitriles. Hydrogenation of benzonitrile over Pd–C affords a mixture of benzylamine and dibenzylamine. However, the product changes markedly with solvent, from predominantly benzylamine (63%) in octane to predominantly dibenzylamine (63%) in benzene.[17] Further, it is noted that benzonitrile is hydrogenated to give an 80% yield of benzylamine (isolated as hydrochloride) in acetic acid over Pd–$BaSO_4$,[57] while dibenzylamine is formed almost exclusively over Rh–C and Pt–C in neutral solvents.[17,19] In contrast to the hydrogenation of aliphatic nitriles, no tertiary tribenzylamine is

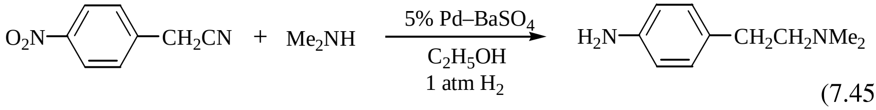
formed over any of these catalysts. Typical results on the hydrogenation to secondary and tertiary amines of some aliphatic nitriles and benzonitrile are shown in Table 7.2.

The platinum-catalyzed hydrogenation of benzonitrile without a solvent in the presence of sufficient water has been shown to be superior for the manufacture of dibenzylamine on a commercial scale.[19] The presence of water in amounts more than 1.0 molar ratio to nitrile eliminated the poisoning of the catalyst. The only significant byproduct was toluene, the yields of which increased from 3–4 mol% at the lower pressures to 8–9% at the higher pressures in the range of 2.1–8.3 MPa H_2. The effect of temperature on product distribution was minor in the range of 40–130°C. A typical run of the hydrogenation is shown in eq. 7.44. Hydrogenation in the presence of much higher ratios of water, however, produced substantial amounts of tribenzylamine. For example, the hydrogenation of 150 g (1.45 mol) of benzonitrile over 3 g of 5% Pt–C in the presence of 1500 g (83 mol) of water at 100°C and 2.1–3.4 MPa H_2 gave 39% of tribenzylamine together with 45% of dibenzylamine.



(7.44)

Hydrogenation of nitriles under conditions favorable for the formation of secondary and tertiary amines can be applied to the synthesis of mixed secondary and tertiary amines. The *N*-substituted phenethylamines were synthesized by hydrogenation of a phenylacetonitrile in the presence of an amine; an example is shown in eq. 7.45.[90]



(7.45)

Rylander and Hasbrouck have shown that the hydrogenation of valeronitrile in the presence of butylamine (MeOH, RT, 0.34 MPa H_2) gives butylpentylamine in high selectivities over Pt–C, Pd–C, and Rh–C.[17] The hydrogenation of benzonitrile in the presence of butylamine gives high yields of butylbenzylamine with Rh–C in octane and with Pt–C in octane, ethanol, or benzene. The yield of butylbenzylamine over Rh–C depends highly on the solvent. Nearly quantitative yield of the mixed amine was obtained in octane while in benzene no butylbenzylamine was formed but dibenzylamine was obtained exclusively. In contrast to the case with butylamine, in the presence of diethylamine no diethylbenzylamine was formed in the hydrogenation of benzonitrile over any palladium, rhodium, and platinum catalysts. It is noteworthy that, in palladium-catalyzed hydrogenation, the presence of diethylamine prevented the formation of dibenzylamine, and benzylamine was produced quantitatively.[17]

A mixed tertiary amine is obtained in high yield in copper-catalyzed hydrogenation of an aliphatic nitrile. Thus, the hydrogenation of lauronitrile over a copper catalyst in the presence of dimethylamine gave *N*,*N*-dimethyldodecylamine in a yield of 95%.[91]

TABLE 7.2 Hydrogenation of Nitriles to Secondary and Tertiary Amines

Nitrile	Catalyst	Medium	T (°C)	H_2 P (MPa)	Selectivity (or Yield) (mol%) Primary Amine	Secondary Amine	Tertiary Amine	Other Products	Ref.
Valeronitrile	Rh/C[a]	MeOH	RT	0.34	0	93	7	—	17
	Rh/C	MeOH	RT	5.2	0	100	0	—	17
	Pd/C[b]	MeOH	RT	0.34	0	16	84	—	17
	Pt/C[c]	MeOH	RT	0.34	4	29	67	—	17
Butyronitrile	Pd/C	H_2O/NH_3	125	3.2–4.1	0	3	97	—	7
	Rh/C	H_2O/NH_3	75–110	3.2–4.1	0	100	0	—	7
	Pt/C	H_2O/NH_3	125	3.2–4.1	0	3	97	—	7
Stearonitrile	$CuO–Cr_2O_3$	—	210	9	7.8	88.1	4.1	—	86
Benzonitrile	Rh/C	Octane	RT	0.34	0	100	0	—	17
	Pd/C	Octane	RT	0.34	63	34	0	—	17
	Pt/C	Octane	RT	0.34	0	94	—	6[d]	17
	Rh/C	H_2O[e]	100–110	6.2–8.3	22	42	—	1[f]	19
	Pd/C	H_2O[e]	100	2.1–3.4	19	49	0	30.3[g]	19
	Pt/C	H_2O[h]	105	3.4–5.5	0	97	0	3[f]	19
	Pt/C	H_2O[i]	100	2.1–3.4	0	45	39	0.9[j]	19

[a]94% conversion.
[b]28% conversion.
[c]21% conversion.
[d]Miscellaneous compounds.
[e]Molar ratio of H_2O to nitrile = 1.05.
[f]Toluene.
[g]30% of toluene and 0.3% of benzamide.
[h]Molar ratio of H_2O to nitrile = 1.0.
[i]Molar ratio of H_2O to nitrile = 57.
[j]0.2% of benzamide and 0.7% of a Schiff base.

Caillault et al. obtained high yields of *N*,*N*-dimethyldodecylamine and *N*-methyldidodecylamine from lauronitrile and hexamethylenetetramine (HMTA) over a reduced nickel catalyst (31% Ni–32% NiO–13% MgO–24% SiO_2) in dodecane at 140°C and 1 atm H_2 (eq. 7.46).[92] When the nitrile was first hydrogenated to give about 95% yield of didodecylamine at 140°C and then HMTA was added to the reaction mixture, *N*-methyldidodecylamine was obtained with a yield of about 90%. Since direct formation of *N*-methyldidodecylamine was not observed in the reaction between didodecylamine and methylamine, it has been suggested that the methyldidodecylamine is formed by the reaction of didodecylamine and the methanimine produced from HMTA.

$$\underset{\substack{3.9\ \text{ml}}}{C_{11}H_{23}CN} + \underset{\substack{7.5\ \text{g}}}{(CH_2)_6N_4} \xrightarrow[\substack{65\ \text{ml dodecane} \\ 140°\text{C},\ 0.1\ \text{MPa}\ H_2,\ 22\ \text{h}}]{0.2\ \text{g Ni catalyst*}} \underset{-}{C_{12}H_{25}NHMe} + \underset{69.4\%}{C_{12}H_{25}NMe_2} + \underset{30.4\%}{(C_{12}H_{25})_2NMe} + \underset{0.2\%}{\text{others}} \tag{7.46}$$

[mol (HMTA/RCN) = 3]

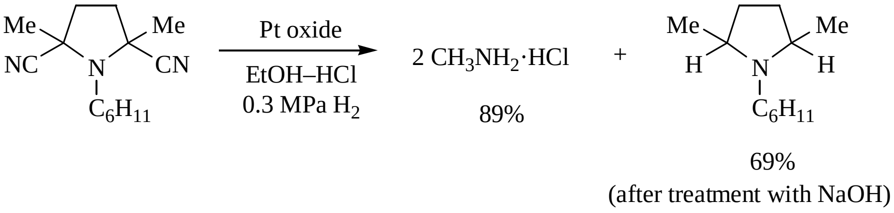
* 31% Ni–32% NiO–13% MgO–24% SiO_2,
prereduced with H_2 at 420°C for 9 h.

7.6 HYDROGENATION ACCOMPANIED BY SIDE REACTIONS

7.6.1 Aminonitriles

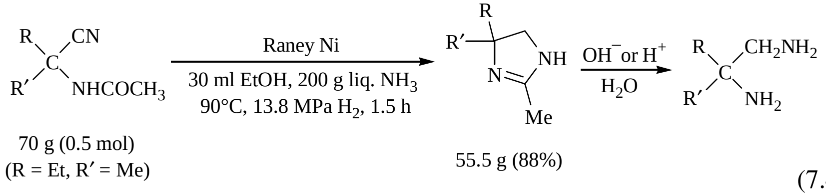
Hydrogenation of α-aminonitriles (R_2NCH_2CN: R = H or alkyl) to the corresponding 1,2-diamines is often accompanied by the hydrogenolysis of the C–CN bond or R_2N–C bond. In the case of *N*-unsubstituted α-aminonitriles, low-pressure hydrogenation in alcoholic hydrogen chloride over platinum oxide gives good yields (60–82.5%) of the corresponding diamine hydrochloride (eq. 7.47).[93] This method, however, is not applicable to *N*-substituted α-aminonitriles. Extensive hydrogenolysis of the C–CN bond took place during the hydrogenation of 1-cyclohexyl-2,5-dicyano-2,5-dimethylpyrrolidine, yielding 89% of methylamine hydrochloride and 69% of 1-cyclohexyl-2,5-dimethylpyrrolidine (eq. 7.48).

$$\underset{\substack{(0.3\ \text{mol, added to} \\ \text{EtOH–HCl at <10°C)}}}{R^1R^2C(NH_2)CN} \xrightarrow[\substack{235\ \text{ml 14\% EtOH–HCl} \\ 0.3\ \text{MPa}\ H_2}]{1\ \text{g Pt oxide}} \underset{60–82.5\%}{R^1R^2C(NH_2)CH_2NH_2\cdot 2HCl} \tag{7.47}$$



(7.48)

According to Reihlen et al., α-aminonitriles undergo decomposition under hydrogenation conditions liberating HCN which may poison the catalyst.[94] The decomposition can be prevented by acetylating the aminonitriles. Thus, α-aminonitriles were hydrogenated in acetic anhydride over platinum oxide and α,β-diacetamino compounds were obtained in high yields. Hawkins and Biggs hydrogenated the monoacetyl derivatives of α-aminonitriles over Raney Ni to form dihydroimidazoles that were hydrolyzed by acid or alkali to yield the corresponding diamines (eq. 7.49).[95]

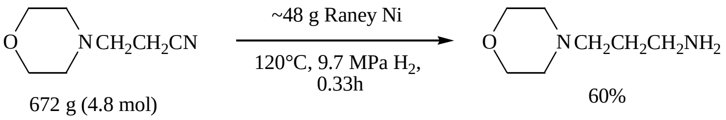


(7.49)

Hydrogenation of *N*-substituted α-aminonitriles with nickel catalyst is labile to hydrogenolysis, resulting in cleavage of the amino group and lower yields of the corresponding amines than in usual nitriles. In the case of α-piperidinocaprylonitrile and α-piperidinophenylacetonitrile the hydrogenolysis was apparently complete and none of the corresponding hydrogenation products were obtained, with the recovery of 80% of piperidine, in the hydrogenation over Raney Ni in ethanol at 80–100°C.[96] However, several successful hydrogenations with Raney Ni have been reported in the presence of ammonia. Baganz and Milster obtained 82 and 79% yields of *N*-(β-aminoethyl)morpholine and *N*-(β-aminoethyl)piperidine in the hydrogenation of the corresponding nitriles with Raney Ni in methanol and ammonia.[97] Various dialkylaminoacetonitriles have been hydrogenated to give 34–88% yields of the corresponding diamines with Raney Ni in ether in the presence of liquid ammonia at 125°C and 8–9.5 MPa H_2.[98] In one patent, it is claimed that the hydrogenation of α-diethylamino- and α-dimethylaminoacetonitriles over Raney Co in cyclohexane- or benzene-ammonia at the temperature below 110°C gives the corresponding diamines in 95 and 80% yields, respectively.[99] Freifelder reports that the hydrogenation of α-dialkylaminonitriles over Rh–Al_2O_3 (10–20% ratio) at room temperature and 0.2–0.3 MPa H_2 gives high yields (68.4–92.5%) of the corresponding diamines in the presence of at least five molar equivalents of ammonia.[100] The hydrogenation, however, was not successful for α-alkylaminonitriles. In the case of α-methylaminoacetonitrile the hydrogen uptake was incomplete and with α-cyclohexylaminoacetonitrile, hydrogenolysis to give cyclohexylamine occurred extensively under these conditions.

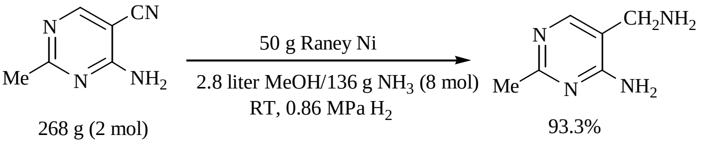
Various β-aminonitriles, which are best prepared by the addition of ammonia, primary amines, or secondary amines to acrylonitrile,[101] were successfully hydrogenated with Raney Ni at temperatures of 90–130°C and 6.7–27 MPa H_2.[102] A typical hydrogenation is shown in eq. 7.50 for β-morpholinopropionitrile. Hydrogenation of the nitrile at 190°C decreased the yield of γ-morpholinopropylamine to 45%. The decrease in the yield may be explained by a reversal of the morpholine-acrylonitrile-

β-morpholinopropionitrile equilibrium at a high temperature. Freifelder obtained good yields of diamines by low-pressure hydrogenations over Rh–Al_2O_3 of β-, γ-, and δ-dialkylaminonitriles.[100]



(7.50)

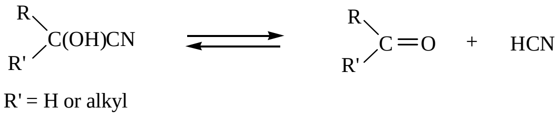
Hydrogenation of some basic nitriles such as 2-methyl-4-aminopyrimidine-5-carbonitrile was not successful in acidic solvents or in the presence of acetic anhydride with palladium or platinum catalysts, because formation of considerably less soluble salt or acetylated product slowed down the hydrogenation.[64] The hydrogenation, however, could be performed smoothly and with an excellent yield over Raney Ni in organic solvents and in the presence of ammonia (eq. 7.51).



(7.51)

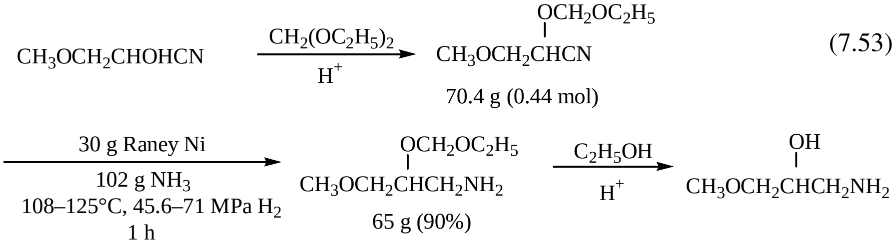
7.6.2 Hydroxy- and Alkoxynitriles

α-Hydroxynitriles (cyanohydrins), which are important intermediates for syntheses of the carboxylic acids, aldehydes, or amines with one more carbon atom than those in starting carbonyl compounds (see, e.g., eq. 7.43), may be decomposed during hydrogenation to the starting carbonyl compounds and hydrogen cyanide, which may poison the catalyst (eq. 7.52). Accordingly, the hydrogenation of cyanohydrins in alkaline conditions should be avoided unless the hydroxyl group is protected by substitution with a group such as an alkyl or an acyl.



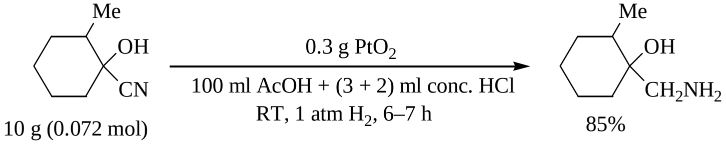
(7.52)

In the Raney Ni catalyzed hydrogenation of 3-methoxy-2-hydroxypropionitrile (methoxyacetaldehyde cyanohydrin), the hydroxyl group had been protected by the reaction with ethylal and a trace of acid to form 2-(ethoxymethoxy)-3-methoxypropionitrile (eq. 7.53), because direct hydrogenation of the cyanohydrin was not successful because of decomposition.[103]



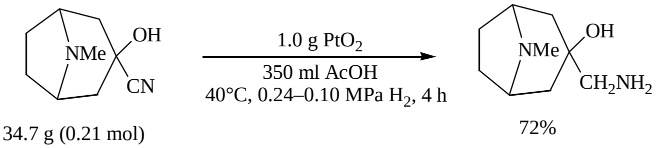
(7.53)

Hydrogenation of cyanohydrins has often been carried out over platinum oxide in acetic acid. Use of freshly prepared or purified substrate is preferable for obtaining reproducible results.[104] The yields of corresponding hydroxyamines appear to depend much on cyanohydrins. Goldberg and Kirchensteiner obtained only a 27.4% yield of 1-hydroxy-1-aminomethylcyclohexane on hydrogenation of cyclohexanone cyanohydrin over platinum oxide in acetic acid because of extensive formation of the corresponding secondary amine.[105] In the presence of a 1.5 molar amount of hydrochloric acid, however, the primary amino product was obtained in nearly doubled amount, although the reaction time was prolonged from 2 h in the absence of hydrochloric acid to 9 h. With the acetate of the cyanohydrin the secondary product that had lost the acetoxyl group was obtained. Tchoubar used platinum oxide, poisoned by carbon disulfide, hydrogen chloride, or hydrogen cyanide, in acetic acid to prevent secondary and tertiary amine formation in the hydrogenation of the cyanohydrins derived from cyclopentanones, cyclohexanones, cycloheptanone, and cyclooctanone, although the rate of hydrogen uptake decreased to one-fifth in the presence of hydrochloric acid, compared to that without the acid.[106] In the presence of concentrated hydrochloric acid in acetic acid, the corresponding hydroxyamines were obtained in 45–60% yields with the cyanohydrins of cyclopentanones, in 70–85% yields with those of cyclohexanones, and in 50% yield with those of cycloheptanone and cyclooctanone, in hydrogenation over platinum oxide at room temperature and atmospheric pressure. The highest yield of 85% was obtained with the cyanohydrin of 2-methylcyclohexanone (eq. 7.54).

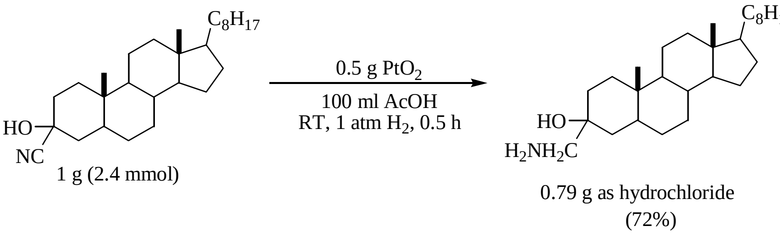


(7.54)

With tropinone cyanohydrin (eq. 7.55)[104] and steroid cyanohydrins (eq. 7.56),[105] however, hydrogenation over platinum oxide in acetic acid in the absence of hydrochloric acid gave satisfactory results.



(7.55)



(7.56)

Cyanohydrins derived from aromatic aldehydes are susceptible to loss of the hydroxyl group due to hydrogenolysis. In the hydrogenation of mandelonitrile over Pd–C in EtOH–HCl, Hartung obtained only phenethylamine and nonbasic byproduct, but no corresponding 2-hydroxyphenethylamine even when the hydrogenation was interrupted at the uptake of 2 mol of hydrogen.[58] Maldelonitriles with an *ortho* substituent, however, were successfully hydrogenated to the corresponding 2-hydroxyphenethylamines over platinum oxide in EtOH–HCl.[107]

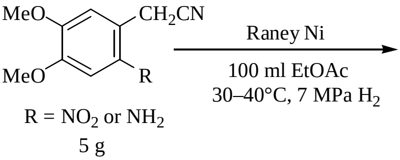
β-Alkoxy- and β-aryloxynitriles, which are readily prepared by cyanoethylation of the corresponding alcohols, are also labile to loss of the alkoxy or aryloxy groups on hydrogenation, just as in the case of β-aminopropionitriles.[102] Accordingly, hydrogenation under mild conditions is recommended for these compounds. Utermohlen obtained various γ-alkoxypropylamines in 50–78% yields in the hydrogenation of the corresponding β-alkoxypropionitriles over Raney Ni at 90–100°C and 5.1–20 MPa H_2 in the presence of liquid ammonia but with no solvent.[108] An example is shown in eq. 7.57. In the case of β-benzyloxypropionitrile, however, the yield of the corresponding amine was only 25%.

$$\underset{210\text{ g }(1.65\text{ mol})}{BuOCH_2CH_2CN} \xrightarrow[\substack{100\text{ ml liq. }NH_3\\ 100^\circ C,\ 10\text{ MPa }H_2,\ 2\text{ h}}]{10\text{–}15\text{ g Raney Ni}} \underset{154\text{ g }(71\%)}{BuOCH_2CH_2CH_2NH_2} \qquad (7.57)$$

Freifelder hydrogenated β-alkoxypropionitriles over Rh–Al_2O_3 at room temperature and 0.2–0.3 MPa H_2 in ethanol in the presence of at least 5 equiv of ammonia and obtained 69–90.5% yields of γ-alkoxypropylamines.[100] In the case of β-methoxypropionitrile, hydrogenation was carried out without solvent at a high pressure (7 MPa H_2) to obtain a high yield (72%) of γ-methoxypropylamine. Hydrogenation at a low pressure was extremely slow in the absence of solvent and, in the presence of a solvent, the volatility of the product amine made removal of the solvent without losing the amine difficult.

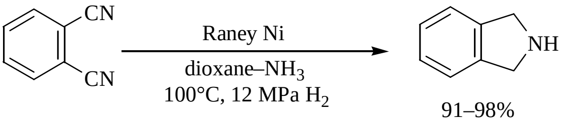
7.6.3 Hydrogenation Accompanied by Cyclization

Primary and secondary γ- and δ-aminonitriles may lead to ring closure to form five- and six-membered compounds, respectively. For example, the hydrogenation of 2-nitro- or 2-amino-4,5-dimethoxyphenylacetonitrile with Raney Ni gives 5,6-dimethoxyindole (eq. 7.58).[109]



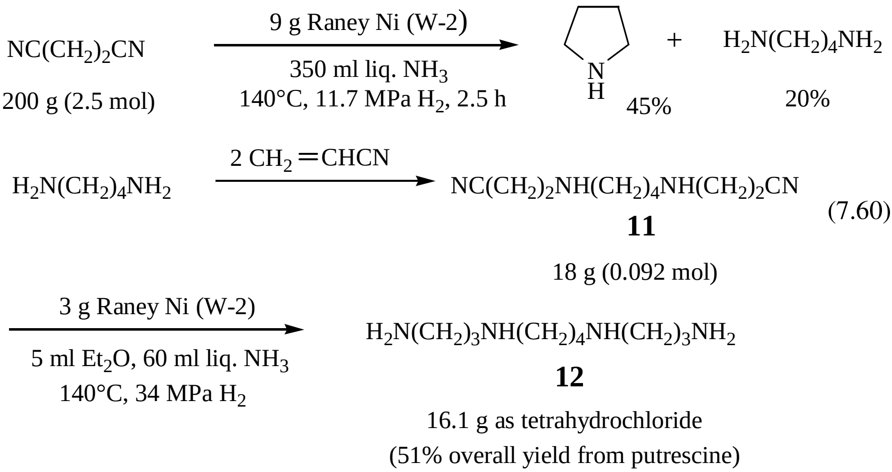
(7.58)

Hydrogenation of phthalonitrile over Raney Ni does not give the corresponding diamine, but isoindoline in 91–98% yields due to extensive occurrence of cyclization (eq. 7.59).[110] Likewise, hydrogenation of succinonitrile and glutaronitrile leads to the formation of pyrrolidines and piperidines, respectively.



(7.59)

Such ring closure occurs especially easily in the case of succinonitrile.[21,110,111] The yield of putrescine (1,4-butanediamine) from succinonitrile was only 20%, and pyrrolidine was the major product in the hydrogenation over Raney Ni at 140°C and 11.7 MPa H_2 even in the presence of ammonia.[111] Putrescine was then cyanoethylated to give *N*,*N*′-bis(2-cyanoethyl)putrescine (**11**), which was hydrogenated under similar conditions to give spermine [*N*,*N*′-bis(3-aminopropyl)-1,4-butanediamine] (**12**) in a 51% overall yield from putrescine as tetrahydrochloride (eq. 7.60). In a patent, a 69.7% yield of putrescine was obtained from succinonitrile in the hydrogenation with a cobalt catalyst at 70°C and 71 MPa H_2 in the presence of a large quantity of ammonia (eq. 7.61).[112]

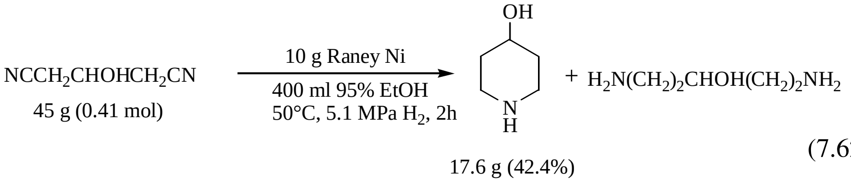


(7.60)

$$\underset{15\text{ g }(0.19\text{ mol})}{NC(CH_2)_2CN} \xrightarrow[\substack{110\text{ g } NH_3\\ 80°C,\ 71\text{ MPa } H_2,\ 1\text{ h}}]{40\text{ g Co catalyst}} \underset{69.7\%}{H_2N(CH_2)_4NH_2} \qquad (7.61)$$

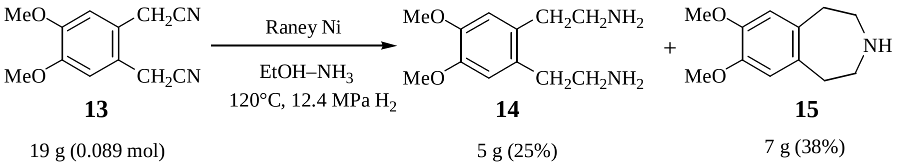
Hydrogenation in a dilute solution is also effective to suppress the cyclization. Thus, when succinonitrile was hydrogenated in THF–NH_3 over Raney Co and CaO at 120°C and 20 MPa H_2, an 88% yield of 1,4-butanediamine was obtained by adding a THF solution of succinonitrile drop by drop during a 100-min period.[113] When hydrogenation was carried out in usual way, the yield of the 1,4-diamine decreased to 72.7%.

Cyclization also occurs extensively with glutaronitriles. In hydrogenation of 1,3-dicyano-2-propanol with Raney Ni, the formation of 4-hydroxypiperidine predominated over the formation of 1,5-diamino-3-propanol even in the presence of liquid ammonia.[114] Hydrogenation in the absence of ammonia further increased the yield of the piperidine (eq. 7.62). Adiponitrile was transformed to azacycloheptane in high selectivity in the hydrogenation over γ-Al_2O_3-supported Ni catalysts in a continuous process at 170°C and 0.1 MPa H_2 in the absence of ammonia.[115]



(7.62)

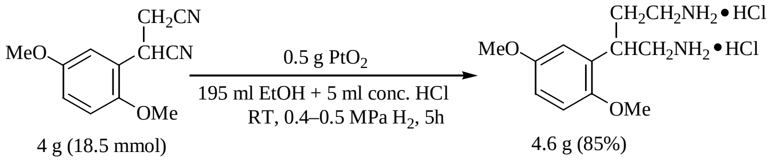
Cyclization occurs readily in the hydrogenation of *o*-phenylenediacetonitrile where the seven-membered benzotetrahydroazepine is formed in 54% yield over a nickel catalyst.[116] Similarly, in hydrogenation of 4,5-bis(cyanomethyl)veratrole (**13**) with Raney Ni, the desired 4,5-bis(2-aminomethyl)veratrole (**14**) was obtained in only a 25% yield together with a 38% yield of the benzotetrahydroazepine **15** (eq. 7.63).[117]



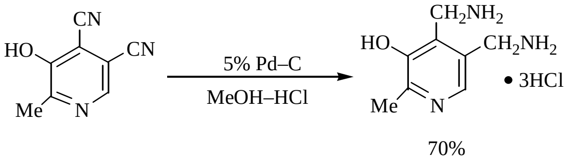
(7.63)

With adiponitrile, an open-chain dinitrile, however, such cyclization leading to a seven-membered cyclic imine occurs to a much lesser extent (see, e.g., eq. 7.25). The hydrogenative cyclizations have been utilized for the synthesis of pyrrolidine and piperidine derivatives from 1,2- and 1,3-dicyano compounds.[118,119]

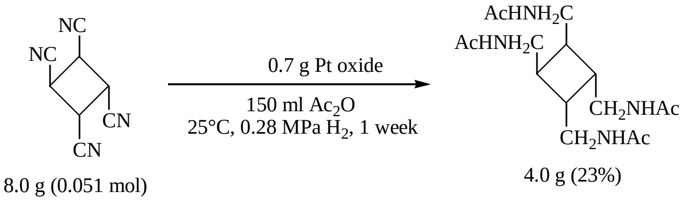
The cyclizations can be depressed in the hydrogenation in strongly acidic media[120–122] or in the presence of an acylating solvent.[123] Examples are shown in eqs. 7.64,[121] 7.65,[122] and 7.66.[123]



(7.64)

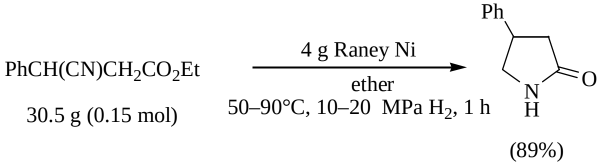


(7.65)

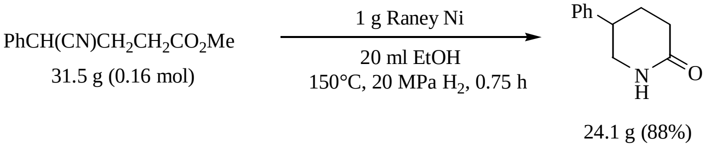


(7.66)

Hydrogenation of β- and γ-cyano esters may give pyrrolidones (γ-lactams) and piperidones (δ-lactams), respectively. Thus, hydrogenation of ethyl β-cyano-β-phenylpyruvate,[96,124] ethyl β-cyanopropionate,[96] and ethyl β-cyano-β-phenylpropionate (eq. 7.67)[96] over nickel catalysts gave the corresponding pyrrolidones. Similarly, methyl γ-cyano-γ-phenylbutyrate was hydrogenated to 5-phenyl-2-piperidone (eq. 7.68), which was further converted to the corresponding piperidine by reduction with sodium and butyl alcohol.[125]



(7.67)



(7.68)

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CHAPTER 8

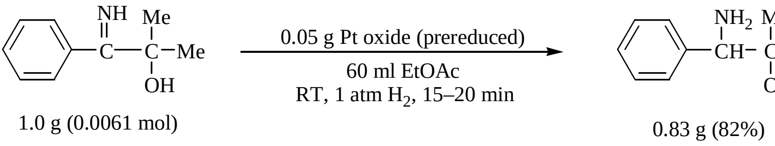
Hydrogenation of Imines, Oximes, and Related Compounds

8.1 IMINES

The hydrogenation of C=N bonds is involved, besides in imines, in the reductive alkylation of ammonia or an amine with a carbonyl compound or in the hydrogenation of the compounds containing unsaturated C–N bonds such as nitriles and oximes. However, C=N bonds may often be hydrogenated more readily in the imines in pure state than in those involved in a reaction mixture as in the reductive alkylation or in the hydrogenation of nitriles and oximes. The hydrogenation of a pure imine may also be advantageous over such a case as in the reductive alkylation, which may be accompanied by a side reaction such as the formation of an alcohol or a condensation product due to the presence of a carbonyl compound. In some cases the reductive alkylation may proceed more effectively when the imines are prepared in situ prior to hydrogenation even without being isolated (see, e.g., eqs. 6.9 and 8.5). A primary imine, or *N*-unsubstituted imine, may react with amine to give the Schiff base and ammonia or with itself to give a hydroamide and may give a mixture of primary and secondary amines on hydrogenation in the same way as in the reductive alkylation of ammonia or in the hydrogenation of nitriles and oximes. Since imines are labile to hydrolysis to produce carbonyl compounds, it is necessary to use an anhydrous solvent at a low temperature in order to hydrogenate them.

8.1.1 *N*-Unsubstituted Imines

Pickard and Vaughan prepared the *N*-unsubstituted imines RC(=NH)R′ derived from the ketones RCOR′ (R = *i*-Pr, *t*-Bu; R′ = *o*-, *m*-, *p*-tolyl) in pure states and hydrogenated these ketimines quantitatively over prereduced Adams platinum catalyst in anhydrous methanol at room temperature and atmospheric pressure,[1] although the yields of the resulting primary amines were not given. In each case the hydrogen absorbed was the theoretical amount. The time required for hydrogenation decreased from *o*- to *m*- to *p*-tolyl in both the *i*-propyl and *t*-butyl series. The *N*-unsubstituted imine derived from α-hydroxyisobutyrophenone was hydrogenated to the corresponding primary amine in high yield over prereduced Adams platinum catalyst in anhydrous ethyl acetate at room temperature and an atmosphere of hydrogen (eq. 8.1).[2] These two examples have a common aspect in that the imines hydrogenated were derived from rather hindered aromatic ketones and it appears that the formation of secondary amines was depressed effectively at low temperature.



(8.1)

8.1.2 Aliphatic *N*-Substituted Imines

Campbell et al. prepared various unsymmetric secondary aliphatic amines in 56–87% yields (33–63% overall yields from starting primary amines) by hydrogenating the corresponding aliphatic *N*-alkylaldimines (RCH=NR′: R = Et, Pr, Bu, *i*-Bu, *i*-Pe; R′ = Et, Pr, Bu, *i*-Pr, cyclohexyl) over prereduced platinum oxide in absolute ethanol in the presence of a small amount of the original primary amine at room temperature and 0.2–0.3 MPa H_2.[3] The aldimines were prepared in 52–83% yields by adding the aldehyde to the amine at 0°C without a solvent and removing the water formed in the reaction with solid potassium hydroxide, followed by distillation from fresh potassium hydroxide. Since the aldimines are unstable and polymerize on standing, they must be hydrogenated within a few hours after distillation. Pd–C may also be used as the catalyst, but the hydrogenation was more rapid and the yields of amine better (56–87%) when prereduced platinum oxide was used. With Raney Ni the calculated amount of hydrogen was taken up rather rapidly, but distillation of the reduction product yielded little or no secondary amine, possibly because of occurrence of predominant side reactions. A typical example is shown in eq. 8.2 for the preparation and hydrogenation of *N*-butylidenepropylamine.

$$CH_3(CH_2)_2CHO + H_2N(CH_2)_2CH_3 \longrightarrow CH_3(CH_2)_2CH{=}NH(CH_2)_2CH_3 \quad (8.2)$$

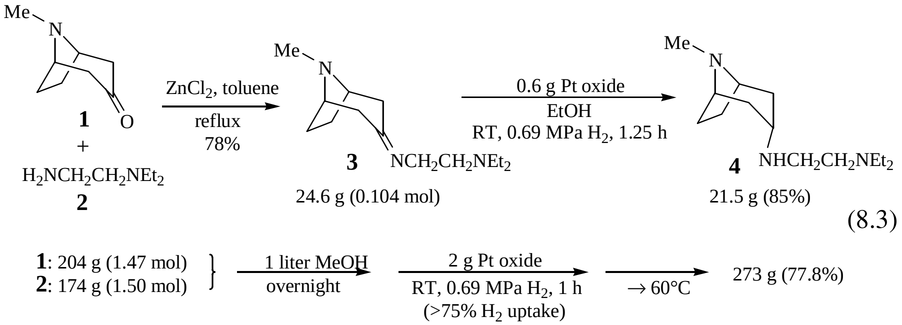
28.8 g (0.4 mol)* 23.6 g (0.4 mol) 70%

* The aldehyde was added to the amine over a period of 2 h at 0°C, the reaction mixture stirred for additional 15 min, water removed with KOH, the organic layer dried overnight over KOH in a refrigerator, then distilled with addition of a few pellets of KOH.

$$CH_3(CH_2)_2CH{=}NH(CH_2)_2CH_3 \xrightarrow[\text{50 ml absolute EtOH/3 ml PrNH}_2\text{; RT, 0.35 MPa H}_2\text{, 0.7 h}]{\text{0.2 g Pt oxide prereduced in 50 ml EtOH}} CH_3(CH_2)_3NH(CH_2)_2CH_3$$

31.6 g (0.28 mol) 20.8 g (64%) (45% overall yield)

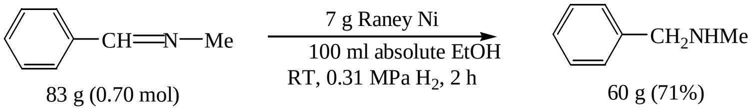
Archer et al. obtained 3α-*N*-(2-diethylaminoethyl)aminotropane (**4**) in 85% yield by hydrogenation of the imine **3**, prepared from the reaction of tropinone (**1**) with 2-diethylaminoethylamine (**2**), over platinum oxide in ethanol at room temperature (eq. 8.3).[4] The same hydrogenation was also carried out over Raney Ni at 60°C and 6.9 MPa H_2. The product was converted directly to the phenyl thioureide without isolating the amine. Compound **4** was also obtained in a 66% yield by hydrogenating the imine **3**, which had been prepared in situ in ethanol by allowing a mixture of **1** and **2** to stand for 2 h, over prereduced platinum oxide mostly at room temperature and finally at 50°C to finish the reaction. In a large-scale run in methanol, a 77.8% yield of **4** was obtained (eq. 8.3). It was noticed that it was not necessary to prereduce Adams platinum oxide when the ketone and the amine were premixed, since the induction period could be eliminated by this procedure.



(8.3)

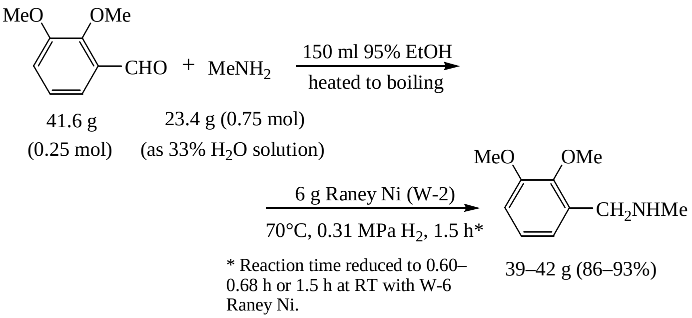
8.1.3 Aromatic *N*-Substituted Imines

Benzydidene alkyl- or arylamines are hydrogenated easily over nickel catalysts to give high yields of the corresponding secondary amines. Benzylidenemethylamine was hydrogenated to *N*-methylbenzylamine in 71% yield over Raney Ni in ethanol at room temperature and 0.31 MPa H_2 (eq. 8.4).[5] Benzylideneisopropylamine was hydrogenated with Raney Ni in ethanol at 90°C and 3.1 MPa H_2 to give an overall yield of 75–79% of *N*-benzylisopropylamine from a starting material for the preparation of the imine.[6]



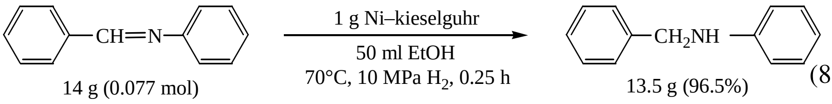
(8.4)

N-Methyl-2,3-dimethoxybenzylamine was also obtained in high yield by preheating to boiling a mixture of methylamine in ethanol and 2,3-dimethoxybenzaldehyde prior to hydrogenation over Raney Ni (eq. 8.5).[7] Similar yields of benzylmethylamines

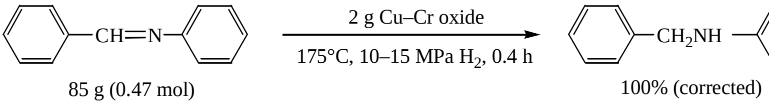


(8.5)

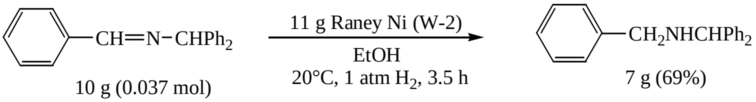
were also obtained from benzaldehyde, anisaldehyde, veratraldehyde, and piperonal. Benzylideneaniline was hydrogenated to *N*-benzylaniline almost quantitatively over Ni–kieselguhr in ethanol at 70°C and 10 MPa H_2 (eq. 8.6)[8] and quantitatively over copper–cronium oxide at 175°C and 10–15 MPa H_2 (eq. 8.7).[9]



(8.6)



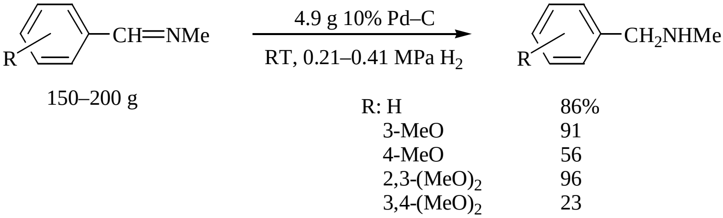
(8.7)



(8.8)

Benzylidenebenzhydrylamine (eq. 8.8) and benzylidene-9-fluorenylamine were hydrogenated to the corresponding secondary amines over Raney Ni in ethanol at 20°C and 1 atm H_2.[10] Similarly, the Schiff bases derived from 1-naphthaldehyde and 2-menaphthylamine (2-naphthylmethylamine) or 2-naphthaldehyde and 1-menaphthylamine were hydrogenated over Raney Ni in high yields (96 and 92%, respectively, as hydrochlorides) to *N*-1-menaphthyl-2-menaphthylamine.[11]

Palladium catalysts were successfully used for the preparation of secondary benzylamines in the hydrogenation of benzylideneamines, although over palladium the products may undergo debenzylation by the structure of benzylamines and also by the reaction conditions. Beck et al. obtained various *N*-methylbenzylamines in 23–91% yields by hydrogenation of the corresponding benzylidenemethylamines over Pd–C at room temperature and 0.21–0.41 MPa H_2 without use of solvent (eq. 8.9).[12] Hydrogen uptake was very rapid. Rather low yields of the benzylamines with 4-methoxy group are noteworthy, compared to the results by Baltzly and Phillips, who obtained *N*-methyl-4-methoxybenzylamine, and *N*-methyl- and *N*-butyl-3,4-dimethoxybenzylamines in 75–80% yields by hydrogenation of the corresponding Schiff bases over Adams platinum catalyst in acetic acid.[13]



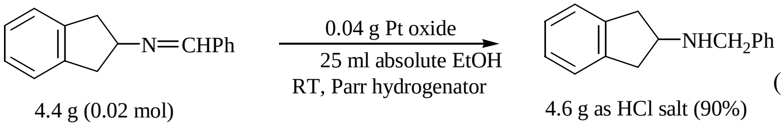
(8.9)

N-Methyl-3,4-methylenedioxybenzylamine, *N*-methyl-2-furylamine, and *N*-methyl-4-dimethylaminobenzylamine were obtained in 68, 35, and 59% yields, respectively, by hydrogenation of a mixture of the aldehyde (0.4 mol) and the amine in a concentrated absolute ethanolic solution over 10% Pd–C (5 g) at room temperature and 0.34 MPa H_2. *N*-3-Methoxybenzyl-β-3,4-dimethoxyphenethylamine was obtained in 91% yield as hydrochloride by hydrogenation of the Schiff base from 3-methoxybenzalde-

$$\underset{231.5\ \text{g (0.9 mol)}}{Ph_2C{=}NPh} \xrightarrow[\text{300 ml benzene; RT, 0.40 MPa } H_2\text{, 2 h}]{\text{9 g 10\% Pd–C}} \underset{203.8\ \text{g (87\%)}}{Ph_2CHNHPh} \quad (8.10)$$

hyde and β-3,4-dimethoxyphenethylamine over Pd–C in anhydrous ethanol, but without isolating the Schiff base.[12] Hydrogenation of benzophenone anil (*N*-phenyldiphenylmethanimine) over Pd–C in thiophene-free benzene gave *N*-benzhydrylaniline in 87% yield (eq. 8.10).[14]

Hydrogenation of *N*-substituted benzylideneamines over platinum oxide often leads to higher yields of the corresponding benzylamines than over Pd–C, as noted above with respect to low yields of *N*-methylbenzylamines with 4-methoxy group over Pd–C.[13,15,16] Thus, 2-benzylamino- (eq. 8.11) and 2-piperonylaminoindanes were obtained in 90 and 96.7% yields, respectively, as hydrochlorides, by hydrogenation of the corresponding Schiff bases over platinum oxide in absolute ethanol at room temperature in a Parr hydrogenator.[15] Similarly, 2-(*p*-methoxybenzyl)aminoindane was obtained in 93.1% yield as hydrochloride by hydrogenation over platinum oxide in acetic acid.

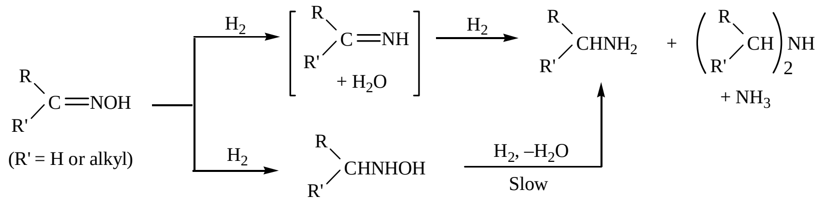


(8.11)

8.2 OXIMES

Hydrogenation of oximes is one of the most useful ways to transform a carbonyl compound into the corresponding amine and has been widely applied to the preparation of a variety of amines from carbonyl compounds. Hydrogenation of oximes to amines usually proceeds through the corresponding imines as intermediates, which may lead to the formation of secondary amine, as in the cases of the hydrogenation of nitriles and the reductive alkylation of ammonia. The imines may be subject to hydrolysis to give carbonyl compounds or alcohols by the action of the water produced together with the imines. On the other hand, ketoximes and their *O*-alkyl derivatives may be hydrogenated to give the corresponding hydroxylamines, especially over platinum catalyst in the presence of 1 equiv of hydrogen chloride.[17,18] Under these conditions, further hydrogenation of the hydroxylamines to amines is usually slow and the hydroxylamines are often obtained in good yields, although acetophenone and benzophenone oximes gave mainly the corresponding amines.[17] With aldoximes, *N,N*-dialkylhydroxylamines tend to be formed.[17,19] Reactions of oximes with hydrogen are illustrated in Scheme 8.1.

With *O*-alkyl ketoxime hydrochlorides, side reactions to give ammonium chloride, a ketone, and an alcohol always accompanied the formation of the *O,N*-dialkylhydroxylamine hydrochlorides, especially in the cases of *O*-methyl- and -ethylacetoxime hydrochlorides, where about 75% of the oximes were transformed into these byproducts. With *O*-methylacetaldoxime, the formation of ammonium chloride was almost quantitative.[18]



Scheme 8.1 Hydrogenation pathways of oximes.

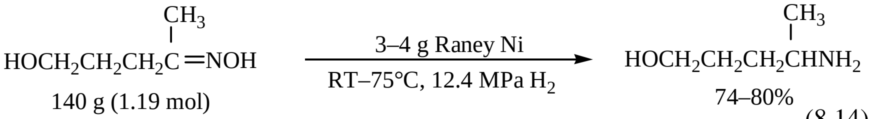
8.2.1 Hydrogenation to Amines

Numerous aliphatic and aromatic oximes have been hydrogenated over nickel catalysts at elevated temperatures and pressures. Winans and Adkins hydrogenated various oximes over Ni–kieselguhr as catalyst at 100–125°C and 10–15 MPa H_2.[8,20] Yields of 62–75% of primary and 10–27% of secondary amines were obtained from the oximes of acetone, valeraldehyde, heptaldehyde, and benzaldehyde. Although hydrogenation of α-benzaldoxime gave a mixture of 77% of benzylamine and 19% of dibenzylamine (eq. 8.12), the oximes of benzophenone (eq. 8.13) and camphor were hydrogenated almost quantitatively to the corresponding primary amines, and no detectable amounts of secondary amines were formed. The oxime of cinnamaldehyde gave only 32% of 3-phenylpropylamine and 12% of bis(3-phenylpropyl)amine owing to the formation of high yields of tar.

$$\underset{\text{40 g (0.33 mol)}}{C_6H_5CH{=}NOH} \xrightarrow[\text{100°C, 10–15 MPa } H_2\text{, 0.75 h}]{\text{3 g Ni–kieselguhr}\ /\ \text{80 ml EtOH}} \underset{\text{27.2 g (77\%)}}{C_6H_5CH_2NH_2} + \underset{\text{6.2 g (19\%)}}{(C_6H_5CH_2)_2NH} \qquad (8.12)$$

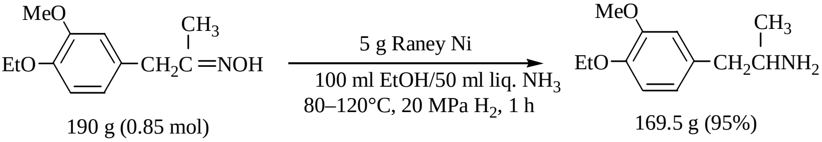
$$\underset{\text{29.6 g (0.15 mol)}}{(C_6H_5)_2C{=}NOH} \xrightarrow[\text{100°C, 10–15 MPa } H_2\text{, 0.75 h}]{\text{2–3 g Ni–kieselguhr}\ /\ \text{70–90 ml EtOH (or } Et_2O)} \underset{\text{95\%}}{(C_6H_5)_2CHNH_2} \qquad (8.13)$$

Raney Ni has been shown to catalyze the hydrogenation of oximes at lower temperatures than Ni–kieselguhr and may be used even at room temperature and a low hydrogen pressure. Since the hydrogenation is highly exothermic, care must be taken to prevent the reaction from becoming too violent, especially in a large-scale run; this can be done by adjusting catalyst to substrate ratio and raising the temperature cautiously, preferably to keep it below 80°C.[21] Such a caution is especially important with oximes that may form condensation products. According to Freifelder, the hydrogenation of 0.1–0.2 molar amounts of cycloheptanone oximes in ethanol at 50–75°C and 10–12.5 MPa H_2 with about 25 wt% of Raney Ni was mildly exothermic, but the same hydrogenation with 1.5 mol of substrate was safely run only with much less amounts of the catalyst (5–10%).[22] A typical run over Raney Ni with a large amount of substrate is given in eq. 8.14, where the temperature was raised cautiously during 30 min to 60°C and eventually to 75°C.[23] Hydrogenation of 1-ethylamino-4-pentanone oxime, however, led to a mixture of 1-ethylamino-4-aminopentane and 1-ethyl-2-methylpyrrolidine in ethanol in the presence of ammonia under similar conditions.



(8.14)

The presence of ammonia may depress the formation of a secondary amine, and quite high yields of primary amines have often been obtained with ketoximes over Raney Ni in the presence of ammonia, as seen in the hydrogenation of 1-(4-ethoxy-3-methoxyphenyl)-2-propanone oxime (eq. 8.15)[24] and 3,3-dimethyl-1-indanone oxime,[25] where the corresponding primary amine was obtained in 95 and 92% yields, respectively.



(8.15)

Reeve and Christian compared Raney Ni and Raney Co (W-7 type) for the hydrogenation of six aliphatic and aromatic aldoximes and ketoximes in the presence or absence of ammonia.[26] From the results summarized in Table 8.1, it is notable that Raney Co gives high yields of primary amine in ethanol or dioxane without addition of ammonia as seen in the results with butyraldoxime, 2-butanone oxime, and acetophenone oxime. On the other hand, Raney Ni usually requires an ammoniacal solvent for best results, with the exception of acetophenone oxime, which gave high yields of primary amine in the absence of ammonia.

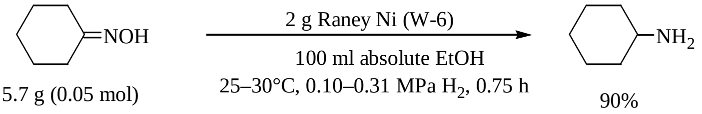
Highly active Raney Ni such as W-5[27] or W-6[28] may be employed for hydrogenation of oximes at low temperatures and pressures, although usually the use of higher ratios of catalyst to substrate is required. Thus, cyclohexanone oxime was hydrogenated to cyclohexylamine in 90% yield at room temperature and 0.10–0.31 MPa H_2 with use of 35 wt% of W-6 Raney Ni (eq. 8.16).[28] Iffland and Yen hydrogenated 10 aliphatic ketoximes over W-5 Raney Ni in 95% ethanol at room temperature and 0.2–0.3 MPa H_2 and obtained the corresponding primary amines in 43–85% yields. The byproducts were the related ketones resulting from hydrolysis, rather than secondary amines.[29] Biel et al. obtained various primary alkyl- and cycloalkylamines by hydrogenation of the corresponding aldoximes and ketoximes over W-5 Raney Ni in 12% alcoholic ammonia at room temperature and 0.41 MPa H_2.[30] A typical run with 2-heptanone oxime is shown in eq. 8.17. Similarly, Ames et al. obtained various alkoxy-1,2,3,4-tetrahydo-2-naphthylamines in 64–75% yields by hydrogenation of the corresponding 2-tetralone oximes over W-7 Raney Ni in ethanol with ammonium hydroxide solution at ~50°C and atmospheric pressure.[31] DeCombe hydrogenated oximes with platinized Raney Ni in the presence of alkali.[32] Rosen and Green obtained higher yields of primary amine in methanolic sodium hydroxide or methanolic sodium methoxide than in the presence of ammonia in the hydrogenation of 2-indanone oxime to 2-aminoindane over Raney Ni at low temperature and pressure.[33] Slightly elevated temperatures (30–60°C) resulted in a more rapid uptake of hydrogen, more effective use of catalyst, and higher yields of product.

TABLE 8.1 Hydrogenation of Oximes over Raney Ni and Raney Co[a,b]

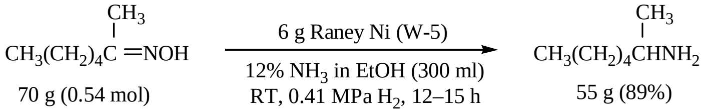
Compound	Catalyst	Solvent	Primary Amine	
			Yield (%)	Purity (%)
$C_3H_7CH{=}NOH$	Raney Co	EtOH	95	97
		EtOH with 3% NH_3	86	96
		Dioxane	86	96
		Dioxane with 1.2% NH_3	92	89
	Raney Ni	EtOH	92	82
		EtOH with 3% NH_3	97	95
		Dioxane	87	91
		Dioxane with 1.2% NH_3	96	94
$C_6H_5CH{=}NOH$	Raney Co	EtOH	84	96
		EtOH with 3% NH_3	91	97
		Dioxane	78	96
		Dioxane with 1.2% NH_3	89	96
	Raney Ni	EtOH	76	96
		EtOH with 3% NH_3	81	98
		Dioxane	88	99
		Dioxane with 1.2% NH_3	68	97
2-Furaldoxime	Raney Co	EtOH	39	96
		Dioxane	43	97
	Raney Ni	EtOH with 3% NH_3	51	96
$C_2H_5C(CH_3){=}NOH$	Raney Co	EtOH	93	97
		Dioxane	96	97
	Raney Ni	EtOH with 3% NH_3	92	95
$t\text{-}C_4H_9C(CH_3){=}NOH$	Raney Co	EtOH	59	97
		Dioxane	50	99
	Raney Ni	EtOH with 3% NH_3	63	99
$C_6H_5C(CH_3){=}NOH$	Raney Co	EtOH	91	83
		EtOH with 3% NH_3	86	90
		Dioxane	87	80
		Dioxane with 1.2% NH_3	87	96
	Raney Ni	EtOH	88	93
		EtOH with 3% NH_3	86	95
		Dioxane	95	96
		Dioxane with 1.2% NH_3	75	94

[a] Data of Reeve, W.; Christian, J. *J. Am. Chem. Soc.* **1956**, *78*, 860. Reprinted with permission from American Chemical Society.

[b] Hydrogenations were carried out under an initial hydrogen pressure of 20–22 MPa with about 2 g of the Raney catalyst (W-7) and 20 or 30 g of the oxime dissolved in 100 ml of solvent. The reaction temperature was chosen to complete the hydrogenation in 10–30 min, and was between 80 and 125°C.

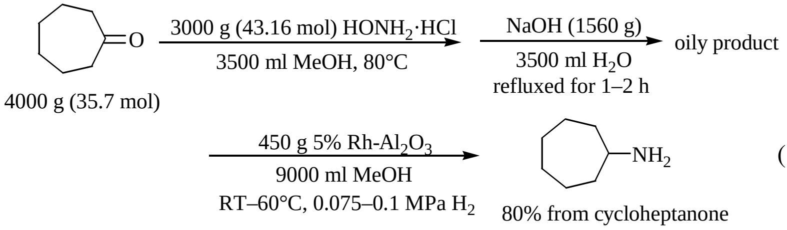


(8.16)



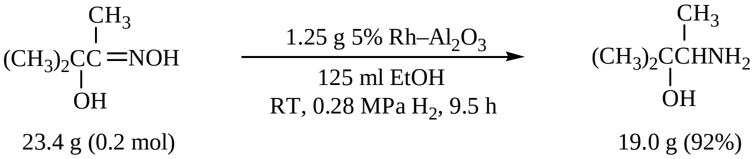
(8.17)

Breitner et al. studied the rate of hydrogenation of cyclohexanone oxime in the presence of four platinum metals (Pd, Rh, Ru, and Pt) supported on carbon in several solvents at room temperature and 0.1 MPa H_2.[34] Although the highest rate was obtained in 0.5*M* aqueous sodium hydroxide solution with 5% Rh–C, the yield of cyclohexylamine was highest (82%) in methanol saturated with ammonia. The yield decreased to 48% in methanol only. Since the yield of secondary amine was in all cases less than a few percent and water must have been formed during hydrogenation, it is presumed that the decrease in the yield might have resulted from the formation of cyclohexanone or its dimethyl acetal as well as their hydrogenation products. Similarly, the products of the hydrogenation of 3-pentanone oxime over 5% Rh–C at 78°C and 6.9 MPa H_2 were a mixture of 50% of 3-aminopentane, 5% of 3-pentanol, and 45% of 3-pentanone even in the absence of solvent, but contained no secondary amine. In contrast, with acetoxime the hydrolysis product was much lesser and secondary amine formation was much greater (~35%) under similar conditions.[35] It has been suggested that the formation of ketones arises by hydrolysis of the intermediate imines and not by hydrolysis of the oximes.[34] On the other hand, Rh–Al_2O_3 has been found to give high yields of primary amine in hydrogenation of some oximes at low pressures even in the absence of ammonia. Thus, Freifelder et al. obtained cycloheptylamine in an overall yield of 80% from cycloheptanone by hydrogenation of the corresponding oxime, prepared in situ, over 5% Rh–Al_2O_3 in methanol without isolating the intermediate oxime (eq. 8.18).[36] It was noted that the reductive amination of cycloheptanone in the presence of Raney Ni and ammonia was accompanied by the formation of a considerable amount of cycloheptanol, which resulted in a decreased yield (61%) of cycloheptylamine. In a smaller-scale run cycloheptanone oxime (25.4 g, 0.2 mol) was hydrogenated to cycloheptylamine in 75% yield in 50 ml of ethanol or methanol at room temperature and 0.2–0.3 MPa H_2 over 5.0 g of 5% Rh–Al_2O_3. The hydrogenation was complete in 1.5–2.0 h.[37]



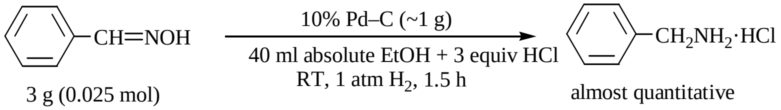
(8.18)

Newman and Lee obtained high yields of amino alcohols by hydrogenation of 3-hydroxy-3-methyl-2-butanone oxime (eq. 8.19) and 1-acetylcyclohexanol oxime over 5% Rh–Al_2O_3 in ethanol at room temperature or at 60–65°C (for the latter oxime) and 0.28–0.34 MPa H_2.[38] The same hydrogenations were unsuccessful over platinum or palladium catalysts.



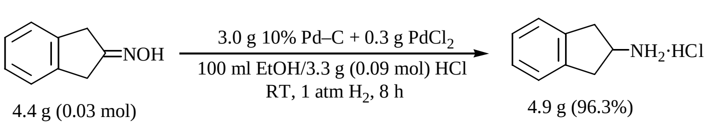
(8.19)

Hartung hydrogenated benzaldoxime with a Pd–C (by Ott and Schröter)[39] in absolute ethanol containing 3 equiv of hydrogen chloride and obtained almost quantitative yield of benzylamine hydrochloride (eq. 20),[40] the same procedure as used for the transformation of benzonitrile to benzylamine except that only 1 equiv, or more, of hydrogen chloride was used in the latter hydrogenation. In the case of benzaldoxime, a mixture of the salts of the primary and secondary bases was formed with 1 equiv of hydrogen chloride.



(8.20)

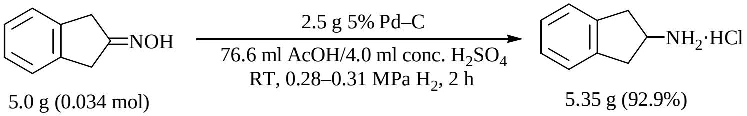
Subsequently, this procedure has been applied to the preparation of numerous primary amines from oximes as well as from nitriles. Levin et al. applied the Hartung's method to the preparation of 2-aminoindane from the corresponding oxime (eq. 8.21).[15] The hydrogenation, however, was successful only with use of an active Pd–C catalyst that had been prepared by reducing palladium chloride with Norit in 0.5 or 1.0*M* aqueous sodium acetate (an improved procedure by Hartung).[41,42] Since the Pd–C catalyst thus prepared was pyrophoric, they employed the catalyst while alcohol-moist to prevent ignition. On the other hand, the Pd–C catalyst with which the hydrogenation was unsuccessful had been prepared by reducing palladium chloride with Norit in distilled water. The resulting Pd–C was washed with water, then with ethanol, and dried with suction. With the latter procedure it might be possible to inadvertently poison the catalyst by some products from the ethanol remaining on the catalyst during the drying process.



(8.21)

Rosen and Green obtained high yields (90–95%) of 2-aminoindane hydrochloride by hydrogenation of 2-indanone oxime over a commercial 5% Pd–C in acetic acid–sulfuric

acid (eq. 8.22),[33] the same medium as used by Rosenmund and Karg for the hydrogenation of 2-hydroxyimino-1-indanone.[43] The decrease in the amounts of catalyst resulted in longer reaction times and decreased yields of the amine hydrochloride. However, by pretreating the acetic acid with the catalyst overnight, the hydrogenation became faster (5–7 h) and more complete, and gave a higher yield (95.2%) of the amine hydrochloride, compared to the case with untreated acetic acid (20–24 h and 86.5% yield), with use of 20 wt% of catalyst.

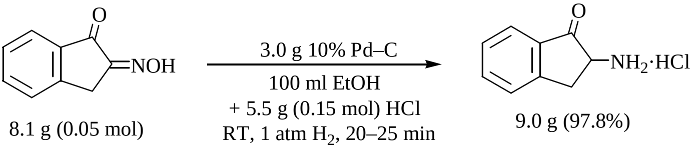


(8.22)

The use of palladium catalyst in neutral solvent was reported in the hydrogenation of benzoin oxime (10 g) over 5% Pd–Al_2O_3 (0.5–1 g) in ethanol (100 ml) at 40–70°C and 0.4 MPa H_2.[44] DL-*erythro*-1,2-Diphenyl-2-aminoethanol was obtained in 84% yield.

In connection to the studies on physiologically active amines related to ephedrine, a number of α-hydroxyimino ketones of the structure ArCOC(R)=NOH have been converted to the corresponding amino ketones or amino alcohols by the method of Hartung.[45–49] The oximino ketones were dissolved in absolute alcohol containing 3 equiv of hydrogen chloride and hydrogenated over Pd–C at 1 atm of hydrogen until hydrogenation practically ceased. The hydroxyimino ketones with Ar = phenyl, *m*- and *p*-tolyl, and naphthyl were all smoothly and completely hydrogenated to the corresponding amino alcohols. In those cases where Ar was substituted by a hydroxyl or methoxyl group, the hydrogenation stopped at the amino ketone hydrochloride stage. The amino ketone was then hydrogenated to the corresponding amino alcohol with new catalyst in aqueous solution.[47]

Levin et al. observed that, in the hydrogenation of 2-hydroxyimino-1-indanone to 2-amino-1-indanol by the general method of Hartung, the first 2 equiv of hydrogen were taken up with ease, but then there was a sharp break in hydrogen absorption and the reaction proceeded only very slowly. At this stage 2-amino-1-indanone hydrochloride was obtained almost quantitatively (eq. 8.23). However, by use of fresh catalyst, hydrogenation to amino alcohol was completed readily at room temperature to give a high yield of 2-amino-1-indanol hydrochloride (eq. 8.24).[41]



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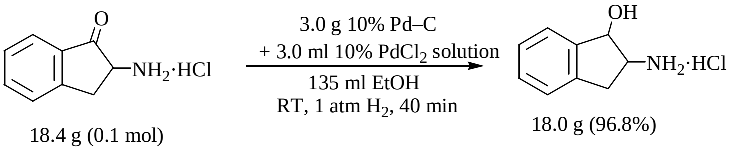

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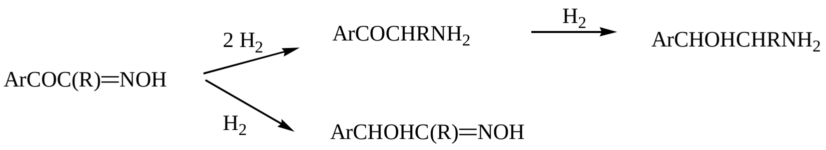
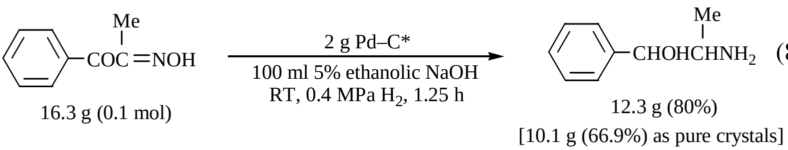


Scheme 8.2 Hydrogenation pathways of α-hydroxyimino ketones.

The hydrogenation of α-hydroxyimino ketones to amino alcohol may follow two courses, which depend on catalyst, substrate, and medium (Scheme 8.2). In the presence of hydrogen chloride the course through an amino ketone as intermediate proceeds rapidly to give the amino alcohol in high yields. At the uptake of 2 mol of hydrogen the intermediate amino ketones are often obtained in high yields.[15,45,47] In neutral alcoholic solution slow hydrogenation through an hydroxyimino alcohol as an intermediate tends to occur. In the case of α-hydroxyiminoacetophenone hydrogenation in neutral alcoholic solution led to the formation of 2,5-diphenylpyrazine (see also Scheme 8.6). Later, however, Hartung and Chang found that the course of the hydrogenation may depend on the preparation of Pd–C catalyst.[50] As was observed with α-hydroxyiminopropiophenone, over a Pd–C catalyst prepared with use of pure palladium chloride, the product at the uptake of 1.8–2.2 mol of hydrogen was a mixture consisting of approximately equal amounts of hydroxyimino alcohol and amino alcohol even in ethanolic hydrogen chloride, in contrast to the previous results that the intermediate products were practically pure amino ketone hydrochlorides. The hydroxyimino alcohol was resistant to further hydrogenation even in the presence of fresh catalysts, more active catalysts, or even catalysts to which promoters had been added. The yields of amino alcohol were improved by the addition of platinum or rhodium to palladium. Alternatively, good yields of amino alcohols were obtained by hydrogenation of α-hydroxyimino ketones in alkaline medium (eq. 8.25).

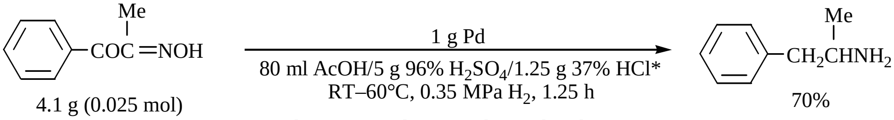


(8.25)

* Prepared from 2 g of Nuchar and 0.2 g of pure $PdCl_2$ in the presence of NaOAc.

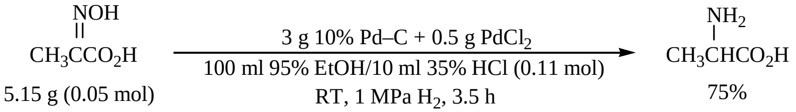
Kindler et al. hydrogenated α-hydroxyiminoacetophenone and α-hydroxyiminopropiophenone (eq. 8.26) to the corresponding phenylalkylamines over a palladium black in acetic acid in the presence of sulfuric acid.[51] The hydrogenolysis of the intermediate amino alcohols proceeded not at all in alcohol and acetic acid, and only rather slowly in acetic acid–sulfuric acid. In contrast, 3-hydroxy-3-phenylpropylamine, with one more carbon atom between the hydroxyl and amino groups, was hydrogenolyzed much faster under these conditions. Perchloric acid may also be used instead of sulfuric acid, but some hydrogenation of the aromatic ring occurred even when the hydro-

genation was interrupted after the calculated amount of hydrogen required for the formation of the phenylalkylamine had been consumed.



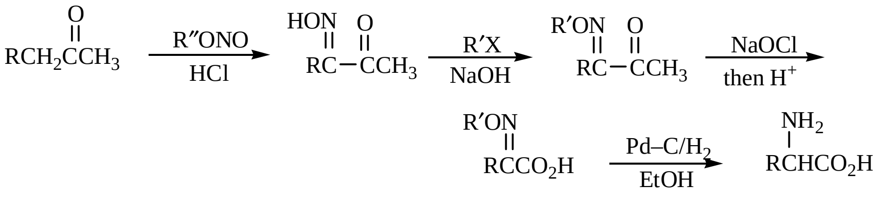
* The same results were obtained without addition of HCl. (8.26)

α-Hydroxyimino acids or esters were hydrogenated to the corresponding amino acids or esters over Pd–C in ethanol containing 2 m equiv of hydrochloric acid.[52] Thus, α-amino acids such as alanine (eq. 8.27), α-aminobutyric acid, norvaline, norleucine, and *O*-methyltyrosine were prepared in 69–89% yields by hydrogenation of the corresponding hydroxyimino acids or esters over Pd–C in ethanol–hydrochloric acid.



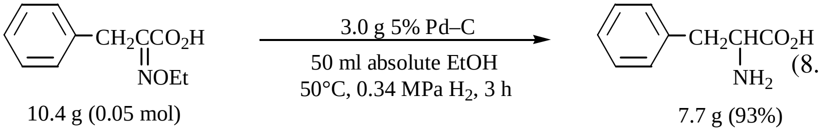
(8.27)

Ferris developed a general synthetic route of α-amino acids from methyl ketones, which involved nitrosation of the ketone, alkylation of the resulting α-hydroxyimino ketone, cleavage of the α-alkoxyimino ketone formed with hypochlorite, and hydrogenation of the resulting α-alkoxyimino acid to an α-amino acid. The reactions sequence is shown in Scheme 8.3.[53] Overall yields of α-amino acids from methyl ketones ranged from 14 to 63%. Hydrogenation of the alkoxyimino acids was carried out over Pd–C in ethanol at 50°C and 0.34 MPa H_2 to give essentially quantitative yields of α-amino acids. In an example shown in eq. 8.28, α-ethoxyimino-3-phenylpropionic acid was hydrogenated to phenylalanine in 93% yield over Pd–C in neutral ethanolic solution. Hydrogenation of the hydroxyimino compound over W-6 Raney Ni in water gave only 43% yield of the amino acid.[54] Ethyl hydroxyiminomalonate was also transformed to aminomalonate in high yield over Pd–C or Pd–Al_2O_3 in etha-



Scheme 8.3 Synthesis of α-amino acids from methyl ketones.

nol (eq. 8.29).[55] This method of hydrogenation was more applicable to a relatively large-scale run than the procedure using a nickel catalyst.[56]



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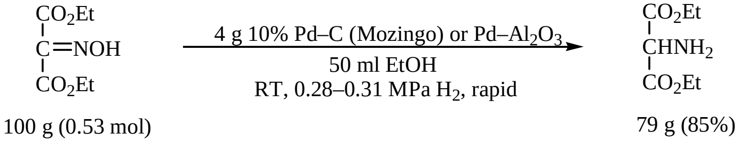
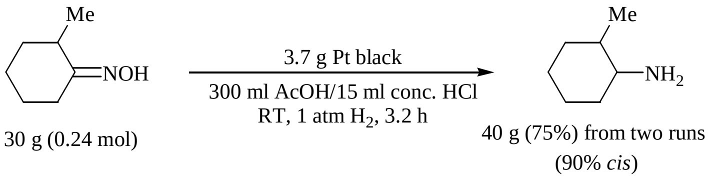


(8.29)

Hydrogenation of oximes over platinum catalyst may lead to extensive formation of secondary amines without solvent[35] or in alcohols[4,33,57–60] as well as in acetic acid.[33,61] Hydrogenation is usually slow and tends to be accompanied by the formation of ketones and alcohols with ketoximes as a result of hydrolysis at the intermediate imines, rather than at the oximes that are hydrolyzed only slowly.[34] The secondary amine formation is especially extensive with the oximes of unhindered ketones and decreases with increasing steric hindrance around the hydroxyimino groups. Thus, the hydrogenation of acetoxime over 5% Pt–C at 75–100°C and 6.9 MPa H_2 gave a mixture consisting of 32% of isopropylamine and 68% of diisopropylamine, while the hydrogenation of 3-pentanone oxime gave 30% of primary amine, 63% of 3-pentanone, and 7% of 3-pentanol, but no secondary amine.[35] Similarly, the oximes of methyl ketones gave primary and secondary amines in hydrogenation over platinum oxide in methanol, but the ketoximes with longer chains gave primary amines only.[57] Hydrogenation of 3-methylcyclohexanone oxime gave bis(3-methylcyclohexyl)amine almost exclusively over platinum in acetic acid.[61] Hückel and Thomas obtained *cis*- and *trans*-3-methylcyclohexylamines (24% *cis*) in 70% yield in the hydrogenation of 3-methylcyclohexanone oxime over a platinum black in acetic acid; however, over platinum oxide the yields of the amine were only 40% in acetic acid and 30% in methanol under the same conditions.[59] Hydrogenation of cyclopentanone oxime over platinum oxide in methanol gave almost pure dicyclopentylamine from which the pure secondary amine was obtained in 80% yield.[58] In this case the best method to obtain cyclopentylamine was the hydrogenation over Raney Ni in methanol at room temperature where 60% of the primary amine and 4% of the secondary amine were isolated. Although the yields of primary amines are not always high, hydrogenation of oximes over platinum has often been employed for the preparation of primary amines, especially in those cases where palladium catalysts are not effective as in hydrogenation of the oximes of alicyclic ketones.[34,62] Freifelder could not hydrogenate the oximes of cyclopentanone, substituted cyclopentanones, cyclohexanone, and cycloheptanone with Pd–C in acidic media.[62] Hydrogenation of 2-methylcyclohexanone oxime over platinum black in acetic acid–hydrochloric acid gave 2-methylcyclo-

hexylamine containing ~90% *cis* isomer in 75% yield (eq. 8.30).[59] Avram et al. obtained ethyl 3-aminocyclobutane-1-carboxylate in 37% yield and diethyl 3-aminocyclobutane-1,1-dicarboxylate in 36% yield by hydrogenation of the corresponding oximes over platinum oxide in ethanol.[60] Archer et al. obtained 5.5 g (26.3%) of 3α-aminotropane from 23 g of tropinone oxime by hydrogenation over platinum oxide in methanol at 50°C (eq. 8.31).[4] However, 6-methoxy-3α-aminotropane was obtained in a better yield (47%) by hydrogenation of the corresponding oxime hydrochloride over Raney Ni in methanol at room temperature and 5 MPa H_2.[63]



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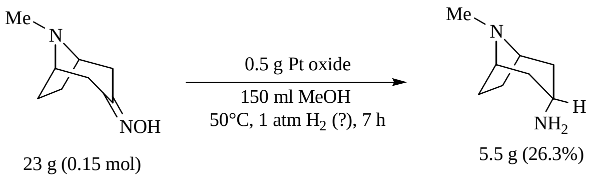
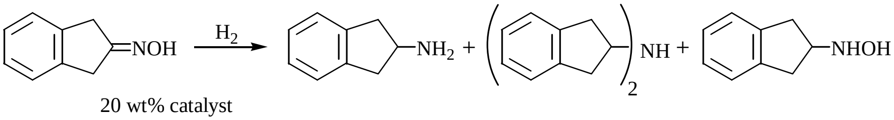


(8.31)

Masamune et al. obtained a 1:2 mixture of *trans*- and *cis*-1-amino-2-phenylcyclohexanes by hydrogenation of 2-phenylcyclohexanone oxime (10 g) over platinum oxide (0.6 g) in acetic acid (500 ml) at room temperature and atmospheric hydrogen pressure for 24 h.[64] Rosen and Green hydrogenated 2-indanone oxime over 5% Pt–C in various solvents.[33] The results shown in Scheme 8.4 indicate that the hydrogenation in the presence of mineral acid tends to produce hydroxyaminoindane, which is further hydrogenated only very slowly. Van Haveren et al. obtained bis(polyhydroxyalkyl)amines in 26–80% yields by hydrogenation of aldose oximes over 5% Pt–C in water at 50°C and 10 MPa H_2.[65] As an example, the hydrogenation of D-galactose oxime under the conditions described above gave bis(D-*galacto*-2,3,4,5,6-pentahydroxyhexyl)amine in 79.5% yield. D-Glucose oxime was hydrogenated much more slowly than the oximes of D-arabinose, D-mannose, and D-galactose, probably because a considerable portion of cyclic forms was present in the solution of glucose oxime, compared to the other oximes. However, when a mixture of D-glucose and D-*gluco*-2,3,4,5,6-pentahydroxyhexylamine was hydrogenated under the same conditions, bis(D-*gluco*-2,3,4,5,6-pentahydroxyhexyl)amine was obtained in 31.6% yield.

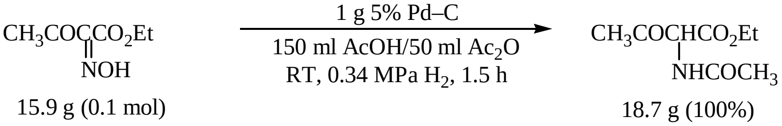
The formation of secondary amine can be largely depressed by hydrogenating oximes in acetic anhydride where acetylated primary amines are formed in high yields. The method has been applied to the hydrogenations over palladium[66,67] and platinum[68,69] catalysts. For example, ethyl α-hydroxyiminoacetoacetate was converted to the acetylamino derivative quantitatively in the hydrogenation over 5% Pd–



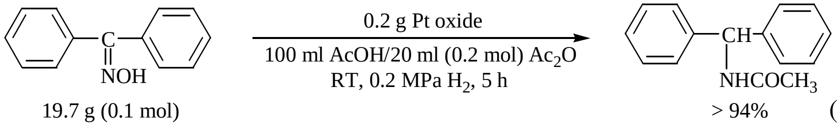
Conditions	Amine	Secondary amine	Hydroxylamine
20 wt% catalyst, EtOH, 32% conversion		15.9%	
100 wt% catalyst, MeOH–HCl		0%	30–35%
20 wt% catalyst, AcOH, 22% conversion	5%	5%	
20 wt% catalyst, AcOH–H_2SO_4 (2.2 mol)			54%

Scheme 8.4 Products of hydrogenation of 2-indanone oxime over 5% Pt–C in various solvents (room temperature; 0.31–0.28 MPa H2).

C in acetic acid–acetic anhydride (eq. 8.32). Similarly, benzophenone oxime was transformed into *N*-acetylbenzhydrylamine in more than 94% yield over platinum oxide in the presence of acetic anhydride (eq. 8.33). An excess acetic anhydride may react with the water formed during the hydrogenation and may thus prevent the formation of ketones by hydrolysis.



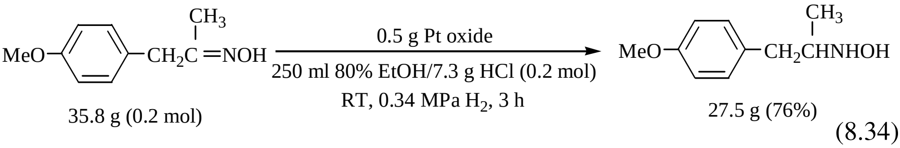
(8.32)



(8.33)

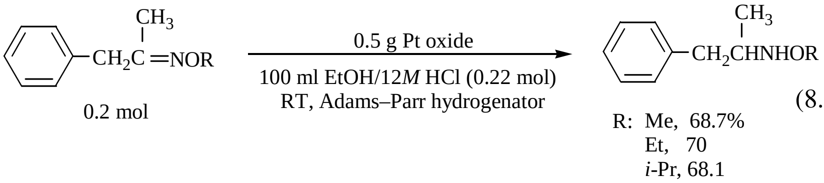
8.2.2 Hydrogenation to Hydroxylamines

Oximes and their alkyl ethers are hydrogenated to the corresponding hydroxylamines and their *O*-alkyl derivatives, respectively, in alcoholic or aqueous alcoholic hydrogen chloride over platinum catalyst.[17,18] Butyraldoxime was hydrogenated to give *N*-butylhydroxylamine, but isobutyraldoxime gave *N,N*-bis(isobutyl)hydroxylamine.[17] *N*-Cyclohexyl-,[70] *N*-cyclopentyl-,[71] and *N*-cyclooctylhydroxylamines[71] were obtained, respectively, in 65, 62, and 31% yields from the corresponding cyclic ketoximes. Benzaldoxime, however, was hydrogenated to a mixture of benzylamine and dibenzylamine.[17] The oximes of acetophenone and benzophenone were hydrogenated to the corresponding primary amines. On the other hand, the oximes of arylmethyl methyl ketones and 2-tetralone were hydrogenated to the corresponding hydroxylamines in 30–78% yields in the hydrogenation over platinum oxide in 80% ethanol or ethanol containing 1 equiv. of hydrogen chloride at room temperature and 0.34 MPa H_2.[72] A typical example is given in eq. 8.34.



(8.34)

O-Alkyl oximes are likewise hydrogenated to the corresponding *O*-alkylhydroxylamines under similar conditions.[18] Solutions of *O*-alkyl oxime hydrochlorides may be prepared either by dissolving the *O*-alkyl oxime in a solution of the calculated amount of hydrogen chloride in 65% alcohol or by adding the calculated amount of the carbonyl compound to a solution of *O*-alkylhydroxylamine hydrochloride in 65% alcohol and allowing the solution to stand for about an hour. Various *O*-methyl- and *O*-ethyl-*N*-alkylhydroxylamines were prepared by hydrogenating the solutions of the *O*-alkyl oxime hydrochlorides over platinum oxide at room temperature and 0.1–0.3 MPa H_2.[18] Under similar conditions 2-alkoxyamino-1-phenylpropanes (alkyl: Me, Et, *i*-Pr) were prepared in good yields from the corresponding *O*-alkyl oximes (eq. 8.35).[73] Similarly, 2-alkoxyamino-1-(3- or 4-pyridyl)propanes were prepared in 22–73% yields from the corresponding *O*-alkyl methyl picolyl ketoximes.



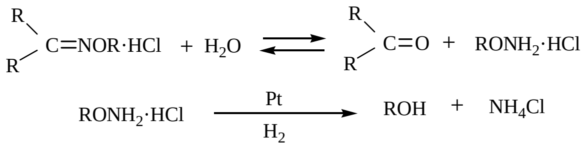
(8.35)

Hydrogenation of *O*-alkyl oximes was always accompanied by the formation of ammonium chloride, a ketone, and an alcohol. In the case of *O*-methyl- and *O*-ethylacetoxime hydrochlorides, about 75% of the oximes were transformed into these byproducts. *O*-Methylacetoxime gave almost a quantitative yield of ammonium chloride.[18] The formation of these products was explained by occurrence of the hydrolysis to give a ketone and *O*-alkylhydroxylamine during hydrogenation. The hydrogenation of *O*-alkylhydroxylammonium chlorides has been shown to proceed readily and most rapidly with *O*-methylhydroxylammonium chloride (see Scheme 8.5). As in the case of benzaldoxime, *O*-methylbenzaldoxime gave no hydroxylamine but instead the hydrochlorides of benzyl- and dibenzylamines.

8.2.3 Hydrogenation Accompanied by Cyclization

Hydrogenation of hydroxyimino ketones or esters may be accompanied by the formation of cyclic products, especially at elevated temperatures, as a result of inter- or intramolecular condensation in the course of hydrogenation.

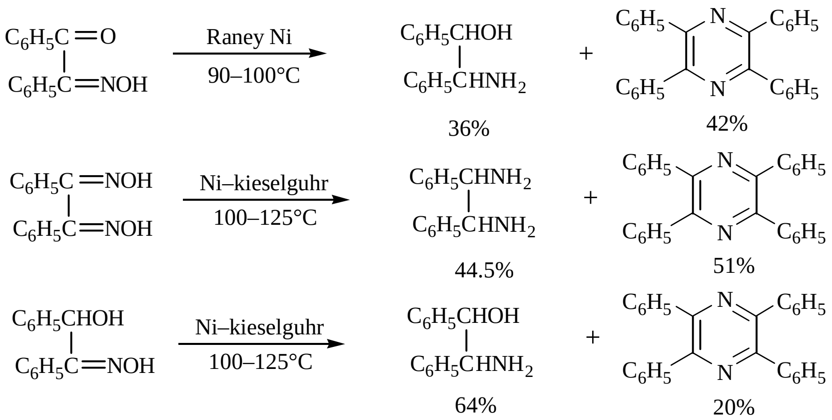
Hydrogenation of α-hydroxyimino ketones and esters, and also of 1,2-dioximes, may lead to the formation of pyrazines. Tetraphenylpyrazine became the predominant product in the hydrogenation of benzil monoxime and dioxime over nickel catalyst in ether or alcohol at around 100°C. The pyrazine was formed even in the hydrogenation



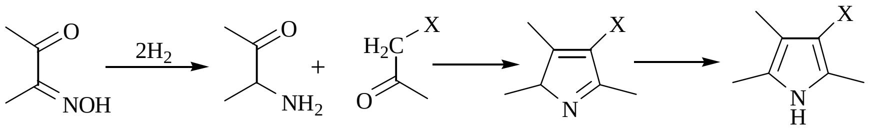
Scheme 8.5 Reactions of *O*-alkyl oxime on hydrogenation.

of benzoin oxime, although in a lesser yield than the corresponding amino alcohol (Scheme 8.6).[20] Hydrogenation of hydroxyiminoacetoacetic ester, -acetophenone, and -indanone gave only the corresponding pyrazines under the same conditions.[21] It is noted that α-hydroxyiminopropiophenone in small amounts (0.1 mol) was hydrogenated rapidly and almost quantitatively to give 2-amino-1-phenyl-1-propanol over nickel at 75–90°C, while with larger amounts (0.5 mol) the formation of compounds of higher molecular weight could not be prevented because of the rise in the reaction temperature.[20]

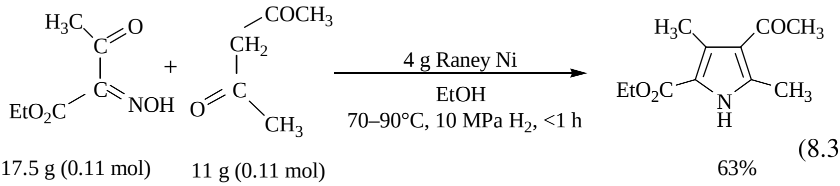
Hydrogenation of an α-hydroxyimino ketone or ester in the presence of a compound with an active methylene group adjacent to a carbonyl group leads to the formation of a pyrrole as a result of the condensation of the intermediate amino ketone with the active methylene compound, just as in the Knorr pyrrole synthesis (Scheme 8.7). For successful formation of pyrroles, it is required that the hydroxyimino group be hydrogenated without affecting the carbonyl group. Thus, eight variously substituted pyrroles were prepared in 23–74% yields in the hydrogenation over Raney Ni in ethanol at 70–90°C and 10 MPa H_2; an example is shown in eq. 8.36.[74]



Scheme 8.6 Formation of tetraphenylpyrazine in the hydrogenation of the oximes of benzil and benzoin (H_2 pressure: 10–15 MPa H_2).

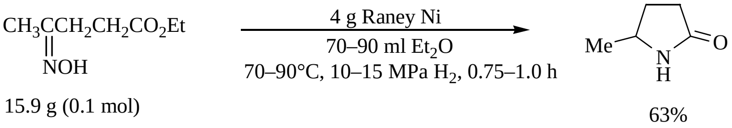


Scheme 8.7 The formation of pyrroles from hydrogenation of an α-hydroxyimino ketone in the presence of a ketone with an active methylene group (X: acyl, alkoxycarbonyl, or cyano).



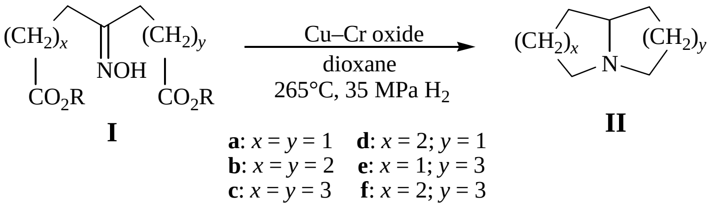
(8.36)

Hydrogenation of γ– and δ-hydroxyimino esters may give 2-pyrrolidones and 2-piperidones, respectively, by intramolecular condensation. Thus, the hydrogenation of ethyl 4-hydroxyiminovalerate over Raney Ni in ether or ethanol at 79–90°C gave 5-methyl-2-pyrrolidone in 63% yield (eq. 8.37).[74] 4-Aryl-4-hydroxyiminobutyric acids gave the corresponding amino acids in the hydrogenation at room temperature, but when the reaction mixture was warmed, 5-aryl-2-pyrrolidones were obtained.[75]



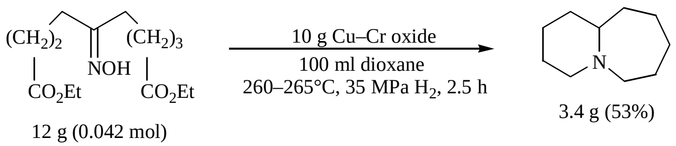
(8.37)

Leonard and Goode used the hydrogenation of hydroxyimino diesters of the structure **I** over Copper–Chromium oxide at 250°C and 36 MPa H_2 for the synthesis of 1-azabicyclo compounds of the structure **II** (Scheme 8.8).[76] By this method pyrrolizidine (**IIa**), octahydropyrrocoline (**IId**), quinolizidine (**IIb**), 1-azabicyclo[5.3.0]decane (**IIe**), 1-azabicyclo[5.4.0]undecane (**IIf**) (eq. 8.38), and 1-azabicyclo[5.5.0]dodecane (**IIc**) were prepared in 50–60% yields. However, attempts to prepare bicyclic amines



Scheme 8.8 Synthesis of 1-azabicyclic compounds from hydroxyimino diesters.

containing larger rings by the hydrogenation of the appropriate hydroxyimino diesters resulted only in the formation of uncyclized products.



(8.38)

Hydrogenation of 1,4- and 1,5-dioximes tends to give pyrrolidines and piperidines, respectively. Thus, the hydrogenation of succindialdehyde oxime over Raney Ni in alcoholic ammonia, which did not occur at room temperature and 10 MPa H_2, afforded only pyrrolidine on warming to 60°C.[77]

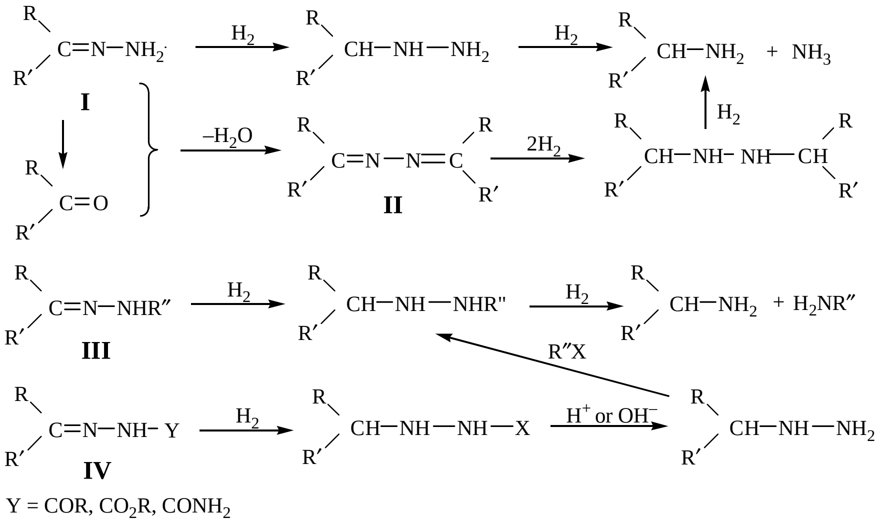
8.3 HYDRAZONES AND AZINES

Hydrogenation of hydrazones and azines is a useful way to prepare hydrazine derivatives. The hydrogenation may proceed further to amines depending on the structure of compound, catalyst, and reaction conditions. Unsubstituted hydrazones (**I**) are liable to hydrolysis, especially with the hydrazones derived from ketones in acidic media and slow hydrogenation. The ketones thus formed may afford azines (**II**) by condensation with the parent hydrazones. Hydrogenation of azines affords symmetrically 1,2-disubstituted hydrazines. In alkyl- or aryl-substituted hydrazones (**III**), such azine formation does not take place and hydrogenation of these hydrazones may lead to unsymmetrically 1,2-disubstituted hydrazines. In contrast to the unsubstituted and alkyl-substituted hydrazones, acyl-, alkoxycarbonyl-, or aminocarbonyl-substituted hydrazones (**IV**) are much more stable to hydrolysis as well as to hydrogenolysis of the N–N bond of the resulting hydrazines. The hydrazines thus formed from **IV** may be transformed to monoalkyl-substituted hydrazines by acid or alkali hydrolysis or to 1,2-dialkyl-substituted hydrazines by hydrolysis followed by alkylation. The reactions of unsubstituted and substituted hydrozones are summarized in Scheme 8.9.

8.3.1 Hydrazones

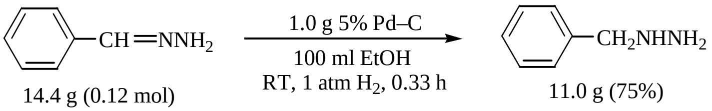
Raney Ni–catalyzed hydrogenation of hydrazones tends to hydrogenolyze the N–N bond of the hydrazine derivatives formed. For example, the hydrogenation of phenylacetone hydrazone (39.3 g, 0.27 mol) in 160 ml of absolute ethanol over 6 g of Raney Ni at 50°C and 0.41 MPa H_2 gave 1-phenyl-2-propylamine in 48.5% yield.[78] The distillation residue was unreacted *N,N′*-bis(1-phenyl-2-propyl)hydrazine. The hydrogenolysis of phenylhydrazones over Raney Ni has been applied to the synthesis of a variety of amino compounds in the sugar series.[79] The hydrogenolysis of hydrazines over Raney Ni has also been proved to be a convenient means producing pure primary and secondary amines starting with mono- and disubstituted hydrazines.[80,81]

A proper choice of catalyst, solvent, and reaction conditions is particularly important in the hydrogenation of an unsubstituted hydrazone of aldehyde or ketone to an



Scheme 8.9 Reactions of unsubstituted and substituted hydrazones with hydrogen.

alkylhydrazine, since the N–N bond of the resulting hydrazine is rather sensitive to hydrogenolysis and there exists a strong tendency to form the azine and its hydrogenation products (see Scheme 8.9). Platinum catalysts have most frequently been used for this type of hydrogenation. Benzaldehyde hydrazone, however, was hydrogenated in high yield to benzylhydrazine over Pd–C in ethanol (eq. 8.39).[82]



(8.39)

Freifelder obtained an 82% yield of benzylhydrazine by hydrogenating a freshly prepared hydrazone over Pd–C in ethanol at 0.3 MPa H_2 in less than 30 min.[83] However, when the hydrazone was allowed to stand for several days to a week, the yield dropped to 45–48%. In the hydrogenation of phenylacetone hydrazone, Biel et al. observed that the formation of large amounts of *N,N′*-bis(1-phenyl-2-propylidene)hydrazine took place when hydrogenation proceeded slowly and incompletely with such catalysts as Pd–C, rhodium, ruthenium, and platinum oxide, and with solvents such as alcohol, water, ethyl acetate, tetrahydrofuran, and dioxane. The *N,N′*-disubstituted hydrazine was obtained when the hydrogenation proceeded slowly to completion, as over platinum oxide in aqueous acetic acid. With Raney Ni in ethanol, the azine and 1-pheny-2-propylamine were formed almost exclusively. 1-Phenyl-2-propylhydrazine was obtained in acceptable yields of 55–70% by use of platinum oxide or supported platinum in alcoholic acetic acid at a pressure of 13.8 MPa H_2. The products obtained over platinum oxide in various conditions are summarized in eq. 8.40.[78]

$$PhCH_2C(CH_3){=}NNH_2 \longrightarrow PhCH_2CH(CH_3)NHNH_2 + PhCH_2CH(CH_3)NH_2 + (PhCH_2CH(CH_3)NH{-})_2 + (PhCH_2C(CH_3){=}N{-})_2 \quad (8.40)$$

Substrate / conditions	$PhCH_2CH(CH_3)NHNH_2$	$PhCH_2CH(CH_3)NH_2$	$(PhCH_2CH(CH_3)NH{-})_2$	$(PhCH_2C(CH_3){=}N{-})_2$
37.0 g (0.25 mol); 1 g Pt oxide, 425 ml EtOH, RT, 3.4 MPa H_2	49.5%		43% (combined)	
37.0 g (0.25 mol); 1 g Pt oxide, 425 ml EtOH, 80°C, 3.4 MPa H_2	38%	46%		
74.1 g (0.50 mol); 0.9 g Pt oxide, EtOH–HCl (0.5 mol), RT, 0.41 MPa H_2	24.2%	34.5%	14% (combined)	
74.1 g (0.5 mol); 10 g Pt oxide, 900 ml EtOH, 300 g (5.0 ml) AcOH, RT, 13.8 MPa H_2	68%		15%	8.5%

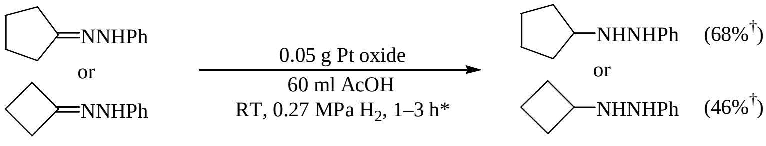
Platinum oxide has also been used for the preparation of monoalkyl- or monoaralkylhydrazines from the corresponding hydrazones.[84,85] It is noted that the yields of hydrazines appear to have been improved considerably with use of ethanol–acetic acid as solvent,[85] compared to the use of methanol.[84]

Hydrogenation of alkyl- or aryl-substituted hydrazones of aldehydes and ketones gives unsymmetric *N,N′*-disubstituted hydrazines. With these hydrazones, the azines are not formed and higher yields of hydrazines than with unsubstituted hydrazones may be expected. Bailey and co-workers obtained high yields of *N,N′*-alkylphenylhydrazines by hydrogenation of the corresponding phenylhydrazones over colloidal platinum (Skita) in aqueous ethanol–hydrochloric acid.[86,87] The phenylhydrozones of acetaldehyde[86] and acetone[87] (eq. 8.41) were converted to the corresponding hydrazines in 95 and 90% yields, respectively, in the hydrogenation over colloidal platinum.

$$(H_3C)_2C{=}NNHPh \xrightarrow[\substack{400\text{ ml }50\%\text{ EtOH/30 ml conc. HCl (0.36 mol)}\\ \text{RT, 0.33–0.1 MPa }H_2\text{, 5 h}}]{\text{colloidal Pt (Skita) (from 10 ml 10\% }H_2PtCl_6)} (H_3C)_2CHNHNHPh \quad (8.41)$$

50 g (0.34 mol) → 90%

Burger et al obtained *N*-cyclopentyl- and *N*-cyclobutyl-*N′*-phenylhydrazines in 68 and 46% yields, respectively, by hydrogenation of the corresponding phenylhydrazones over platinum oxide in acetic acid (eq. 8.42).[88] The hydrogenations were interrupted after the uptake of 1 equiv of hydrogen. Overberger and DiGiulio used ethanol as solvent in the hydrogenation of some α-alkylbenzylhydrazones over platinum oxide to 1-alkyl-2-α-alkylbenzylhydrazines, although the hydrogenations required rather long reaction times (1–5 days).[89]

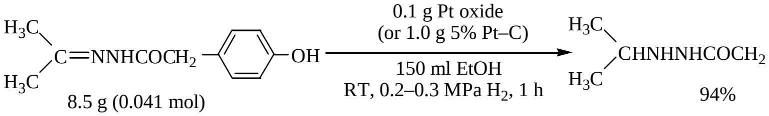


(8.42)

* Hydrogenation interrupted after uptake of 1 mol H_2.

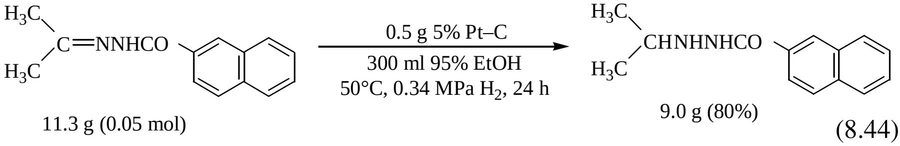
† The yields from starting ketones.

Hydrazones derived from a carbonyl compound and the hydrazine with an acyl, an alkoxycarbonyl, or carbamoyl group (formula **IV** in Scheme 8.9) are rather stable toward hydrolysis as well as hydrogenolysis of the resulting hydrazine. The formation of an azine is also depressed. Therefore, the hydrogenation of these types of hydrazones may give high yields of the corresponding hydrazines. Bettinetti prepared a number of aroylhydrazines, RR′CHNHNHCOAr where R = H, Me, Et, Ph; R′ = Me, Et, *i*-Pr, *i*-Bu, benzyl, Ph, *p*-MeC_6H_4; Ar = Ph, *p*-$MeOC_6H_4$, by hydrogenation of the corresponding aroylhydrazones over platinum oxide or Pd–C at room temperature and atmospheric pressure. Over platinum oxide, higher yields (60–89%) of hydrazines were obtained in anhydrous ethanol than in acetic acid. With the hydrazones where R′ is phenyl or *p*-methylphenyl, high yields (78–95%) of hydrazines were obtained over Pd–C in ethanol.[90] Freifelder also obtained high yields (75–94%) of the hydrazines, $Me_2CHNHNHCOR$ where R was alkyl, cycloalkyl, phenyl, and nuclear-substituted phenyl, by hydrogenation of the corresponding isopropylidenehydrazines over platinum oxide or Pt–C in ethanol.[91,92] An example is shown in eq. 8.43.[92]



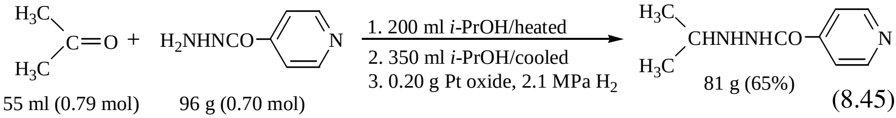
(8.43)

Weinswig and Roche hydrogenated various aroyl- and arylacetylhydrazones of acetone, $Me_2C{=}NNHCOR$ where R = phenyl, benzyl, 1-naphthyl, 2-naphthyl, 1-naphthylmethyl, and 2-naphthylmethyl, over 5% Pt–C in 95% ethanol at 50°C and an initial hydrogen pressure of 0.34 MPa, and obtained the corresponding isopropylhydrazides in 74–83% yields.[93] An example is given in eq. 8.44 for the hydrogenation of 2-naphthoylhydrazone of acetone.



(8.44)

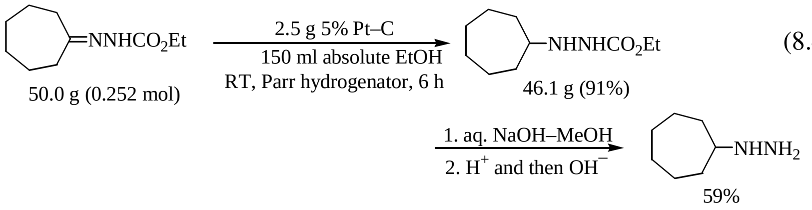
Yale et al.[94] and Fox and Gibas[95] prepared various isonicotinylhydrazine derivatives by hydrogenation of the corresponding isonicotinylhydrazones over platinum oxide in water, ethanol, or acetic acid[94] and in methanol.[95] According to Fox and Gibas, the use of Raney Ni was unsuccessful in all the hydrogenations. The straight- and branched-chain alkylidene and the cycloalkylidene derivatives were most easily hydrogenated. In the case of benzylidene derivatives, however, the presence of an acid medium was required. In some cases the hydrazine derivatives were more conveniently prepared from a mixture of isonicotinylhydrazine and a ketone without isolating the intermediate alkylidene derivative, as described in eq. 8.45.[95]



(8.45)

Hydrogenation of both 1-*o*-chloro- and 1-*p*-chlorobenzoyl-2-isopropylidenehydrazines was successful without causing dehalogenation with use of 5% Pt–C in ethanol, whereas over Pd–C there was evidence that the hydrogenolysis occurred.[96] In the hydrogenation of *o*-bromobenzoyl derivative, a high yield of the corresponding hydrazine could be obtained by reducing the catalyst to substrate ratio from 10% to 2.5%, which was effective to keeping debromination at a very low level.

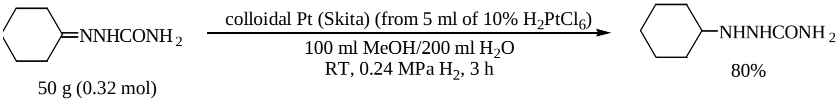
Monosubstituted hydrazines may be prepared in high yields via the hydrogenation of alkoxycarbonylhydrazones, followed by alkaline hydrolysis.[97,98] The hydrogenation of 1-ethoxycarbonyl-2-isopropylidenehydrazine over 5% Pt–C in ethanol gave a 91% yield of the corresponding hydrazine, which was hydrolyzed with 30% aqueous sodium hydroxide at 95–105°C to give 95% yield of isopropylhydrazine.[97a] By the same process cyclohexyl-,[97b] ethyl-,[97c] and benzylhydrazines[97d] were prepared in high yields. Cycloheptylhydrazine, which could not be obtained by the hydrogenation of cycloheptylidenehydrazine over platinum oxide in ethanol because of an extensive formation of the azine, was successfully prepared through hydrogenation of cyloheptanone ethoxycarbonylhydrazone over 5% Pt–C in ethanol, followed by basic hydrolysis in an aqueous sodium hydroxide–methanol mixture. With acidification cycloheptylhydrazine was formed with an evolution of carbon dioxide (eq. 8.46).[98] The ethoxycarbonylhydrazones of 2-indanone and 2-tetralone were hydrogenated to the corresponding hydrazines in 83 and 61% yields, respectively, over 5% Pt–C in ethanol–acetic acid or in ethanol alone.[99]



(8.46)

Semicarbazones derived from various ketones were hydrogenated to the semicarbazides in 76–100% yields over colloidal Pt (Skita) in aqueous methanol in the presence of hydrochloric acid, which facilitated the hydrogenation greatly.[100,101] An optimal amount of hydrochloric acid required, however, varied greatly with the semicarbazone hydrogenated. In the case of cyclohexanone semicarbazone, the hydrochloric acid liberated from the platinic chloride was sufficient for completion of the hydrogenation (eq. 8.47). With carvone, camphor, and menthone semicarbazones the presence of half of the calculated amount of hydrochloric acid was necessary while in the cases of acetone and fenchone semicarbazones, it was necessary to employ the calculated amount of hydrochloric acid for obtaining maximum yields. In one patent, 2-heptylhydrazine was prepared by hydrogenation of 2-heptanone semicarbazone over 5% Pt–C in etha-

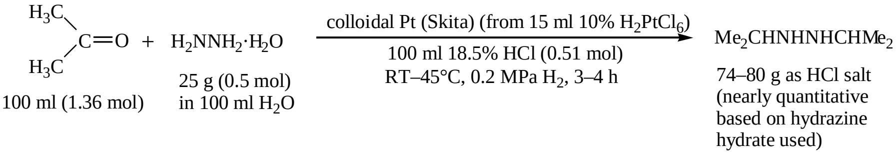
nol–acetic acid and hydrolyzing the resulting semicarbazide with 80% sulfuric acid heated on a steam bath.[102]



(8.47)

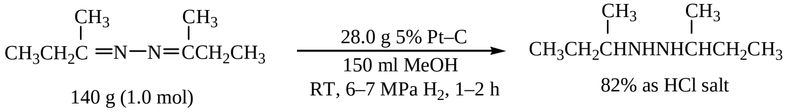
8.3.2 Azines

The hydrogenation of the azines derived from 2 mol of aldehyde or ketone and 1 mol of hydrazine may be used for the preparation of *sym*-1,2-disubstituted hydrazines. The hydrogenation proceeds only slowly in neutral solvent and is accelerated by acid. However, yields of the hydrazines may be decreased by hydrolysis of azines as well as by hydrogenolysis of the resulting hydrazines. Lochte et al. obtained 1,2-bis(isopropyl)hydrazine in a yield over 90% in hydrogenation of the corresponding ketazine over colloidal Pt (Skita) in an aqueous solution in the presence of the theoretical amount of hydrochloric acid. Since the ketazine was not hydrolyzed appreciably by dilute acid under the conditions used, the bis(isopropyl)hydrazine was prepared in nearly quantitative yields (as hydrochloride, based on hydrazine hydrate used), by hydrogenating a mixture of 1 mol of hydrazine hydrate, 1 mol of hydrochloric acid, and 2 mol of acetone in water at room temperature and atmospheric pressure (eq. 8.48).[103] Taipale hydrogenated the same ketazine over a platinum black in acetic acid and obtained a 90% yield of the corresponding hydrazine.[104]



(8.48)

On the other hand, the hydrogenation of isobutyraldazine in acetic acid gave only low yields of *sym*-bis(isobutyl)hydrazine because of the formation of amine and ammonia. However, the yield was improved to 80% in hydrogenation in alcohol or ether containing an equivalent amount of acetic acid. Hydrogenation of the ketazine under these conditions gave a 95% yield of the hydrazine.[104] Freifelder hydrogenated 1,2-bis(1-methylpropylidene)hydrazine in methanol over 5% Pt–C at room temperature and 6–7 MPa H_2 and obtained the corresponding 1,2-dialkylhydrazine in 82% yield (as hydrochloride) (eq. 8.49).[105] The same hydrogenation at room temperature and 0.3 MPa H_2 took 10–12 h, and the yields were lower (40–50%). In contrast, although hydrogenation required 48 h, *N,N′*-bis(isopropyl)hydrazine was obtained in 80% yield by hydrogenation of the corresponding azine over 3 wt% of platinum oxide in methanol at room temperature and 0.3 MPa H_2.



(8.49)

Fox and Gibas hydrogenated benzalazine, 1,2-bis(benzylidene)hydrazine, over platinum catalyst in 8*M* ethanolic hydrogen chloride at room temperature and 0.34 MPa H_2. By stopping the hydrogenation with uptake of 2 equiv of hydrogen, an excellent yield of 1,2-dibenzylhydrazine hydrochloride was obtained.[106] The same azine and its *p,p′*-dimethoxy derivative were also hydrogenated over 2% Pd–$CaCO_3$ in ethyl acetate and 20% Pd–C in methanol, respectively.[107]

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CHAPTER 9

Hydrogenation of Nitro, Nitroso, and Related Compounds

9.1 HYDROGENATION OF NITRO COMPOUNDS: GENERAL ASPECTS

The nitro groups, especially those attached to aromatic rings, are among the most reactive functions toward both chemical and catalytic reductions, and can be reduced with various reducing agents, including hydrogenation catalysts. Catalytic hydrogenation has been frequently employed as the most preferred method for the synthesis of amines from nitro compounds, because in most cases the nitro group is hydrogenated readily over usual transition metal catalysts, separation of the products is simple, and very pure amines are obtained in high yields. The hydrogenation, however, is highly exothermic (~493 kJ or 118 $kcal \cdot mol^{-1}$ in the case of nitrobenzene); therefore, the reaction temperature must be controlled carefully, especially in a large-scale run.

9.2 ALIPHATIC NITRO COMPOUNDS

9.2.1 Hydrogenation Kinetics

A kinetic study by Smith and Bedoit, Jr. has shown that the hydrogenation of aliphatic nitro compounds over Adams platinum oxide in acetic acid was first-order with respect to the concentration of nitroalkane and zero-order with respect to hydrogen pressure, while over Raney Ni in ethanol the kinetics was zero-order with respect to the concentration of nitroalkane and first-order with respect to hydrogen pressure.[1] In contrast, the hydrogenation of aromatic nitro compounds was zero-order in the concentration of the compound and first-order in hydrogen pressure over both platinum oxide and Raney Ni. The rates of hydrogenation of typical aliphatic nitro compounds are summarized in Table 9.1 in comparison with those for nitrobenzene.[1,2] The great differences in rate between nitroalkanes and nitrobenzene over platinum and the rather small differences over Raney Ni are probably related to the differences in the kinetics over the two metals, which appear to indicate that nitroalkanes are only weakly adsorbed on platinum and rather strongly adsorbed on Raney Ni while nitrobenzene is adsorbed strongly on both platinum and Raney Ni. It is also noted that the 2-nitro compounds are hydrogenated much more slowly than the 1-nitro compounds. The rates of hydrogenation of nitropropane over 5% Pd–C, 5% Rh–C, and 5% Pt–C in methanol were also reported to be only $\frac{1}{8}$th–$\frac{1}{30}$th of those for nitrobenzene at room temperature and atmospheric pressure.[3] Under the same conditions nitromethane was not hydrogenated over 5% Ru–C.

TABLE 9.1 Rates of Hydrogenation of Niroalkanes over Platinum Oxide and Raney Nickel

	Rate of Hydrogenation (ml H_2·g cat^{-1}·min^{-1})		
Compound	Pt Oxide[a,b]	Raney Ni[a,c]	Raney Ni[d,e]
Nitromethane	10.2	10.5	13.8–10.9
Nitroethane	6.9	16.1	23.0–18.2
1-Nitropropane	5.4	12.7	20.6–16.3
2-Nitropropane	1.6	10.5	14.2–11.2
1-Nitrobutane	6.0	11.9	—
2-Nitrobutane	0.64	9.7	—
Nitrobenzene	3050	18.4	40.0–31.6

[a]Smith, H. A.; Bedoit, Jr., W. C. in *Catalysis*; Emmett, P. H., Ed.; Reinhold: New York, 1955; Vol. 3, p 149.

[b]Rate constant $k_{1.0}$ for 1 ml of nitro compound in 50 ml AcOH at 30°C.

[c]Rate constant $k_{1.0}$ for 1 ml of nitro compound (0.5 ml in the case of mitromethane) in 50 ml EtOH at 30°C and around 0.34 MPa H_2.

[d]Data of Samuelsen, G. S.; Garik, V. L.; Smith, G. B. L. *J. Am. Chem. Soc.* **1950**, *72*, 3872. Reprinted with permission from American Chemical Society.

[e] Calculated from the amounts of hydrogen absorbed in 100 s over 3.0–3.8 g of Raney Ni with 0.05 mol of nitro compound in 150 ml 95% EtOH at room temperature and atmospheric pressure. A small temperature rise was usually encountered during each reaction, an increase amounting to about 10°C in the case of the very fast reactions.

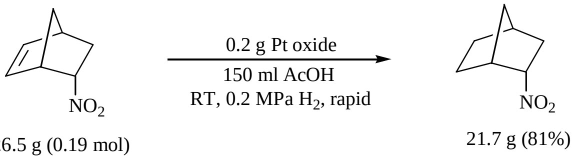
9.2.2 Hydrogenation to Amines

Johnson and Degering hydrogenated all the nitroalkanes available from the nitration of C_1–C_4 hydrocarbons to the corresponding amines over Raney Ni in methyl or ethyl alcohol at 40–50°C and 0.6–11 MPa H_2.[4] Under these conditions, nitromethane, nitroethane, 1- and 2-nitropropane, 1- and 2-nitrobutane, and 1- and 2-nitro-2-methylpropane (0.25–0.33 mol) were hydrogenated in 175 ml methyl or ethyl alcohol over 7.5 g Raney Ni for 2–5 h to afford 82–94% conversions to the corresponding amines. The conversions further increased to 93–97% in the presence of ferric chloride. Iffland and Cassis, Jr. hydrogenated nitroalkanes from C_1 to C_4 over platinum oxide in 95% ethanol at room temperature and 2–3 MPa H_2 and obtained good conversions to the corresponding amines in 9 h (eq. 9.1).[5] In the case of nitromethane, however, hydrogenation proceeded more slowly than in the other nitro compounds, and 38 h was necessary with use of twice the usual amount of catalyst for absorption of 91% of the required amount of hydrogen. The conversion to amine or the time required was not affected by the addition of a trace of hydrochloric acid, but the hydrogenation was retarded by the addition of acetic acid.

$$\underset{(0.2\text{ mol})}{RNO_2} \xrightarrow[\text{100 ml 95\% EtOH; RT, 0.2–0.3 MPa } H_2\text{, 9 h}]{\text{0.1 g Pt oxide}} RNH_2 \qquad (9.1)$$

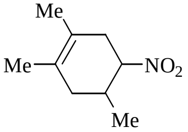
R	Conversion by titration (%)	Yield isolated (%)
R = Me	48	
Et	79	
Pr	83	69
i-Pr	88	64
Bu	91	76

Nitroalkenes with an isolated carbon–carbon double bond are usually hydrogenated first at the carbon–carbon double bond over platinum oxide in acetic acid to give nitroalkanes.[6] On the other hand, over palladium and nickel catalysts the nitro group tend to be hydrogenated first. For example, the hydrogenation of *endo*-5-nitronorbornene over platinum oxide in acetic acid gave *endo*-2-nitronorbornane in 81% yield (eq 9.2).[6e] The uptake of hydrogen was so rapid as to require several pauses for cooling of the reaction mixture and practically ceased after the absorption of 1 equiv.

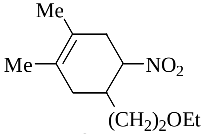


(9.2)

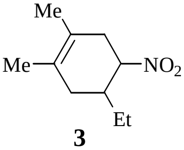
Similarly, in the hydrogenation of 1,2,4-trimethyl-5-nitrocyclohexene (**1**) and 4-(2-ethoxyethyl)-1,2-dimethyl-5-nitrocyclohexene (**2**) over Adams platinum oxide in acetic acid, 1 equiv of hydrogen was taken up rapidly and then the rate of hydrogen absorption became very slow. On the other hand, over 10% Pd–C no abrupt change in the rate of hydrogen absorption was observed in the hydrogenation of **2** and 4-ethyl-1,2-dimethyl-5-nitrocyclohexene (**3**).[7] When hydrogenation of **3** was stopped after 3 equiv of hydrogen had been absorbed, only the saturated amine could be isolated.



1

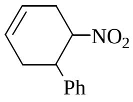


2

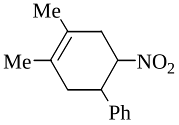


3

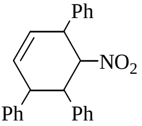
Nightingale and Tweedie hydrogenated the 4-nitrocyclohexenes, obtained by the addition of nitrostyrene to butadiene (**4**), 2,3-dimethylbutadiene (**5**), and 1,4-diphenylbutadiene (**6**), respectively, to the corresponding cyclohexenylamines in nearly quantitative yields, except for mechanical losses, over Raney Ni in methanol at low temperatures and 20 MPa H_2 (0.3 MPa H_2 for **4**).[8] The nitro group except in **4** was hydrogenated first at sufficiently lower temperatures (50°C for **5** and 67°C for **6**) to allow the selective hydrogenation even at 20 MPa H_2. The olefinic double bond in **5** did not hydrogenate below 165°C, and that in **6** required 85°C for hydrogenation. Hydrogenation of **4** at 20 MPa H_2 gave a mixture of the unsaturated and saturated amines at 50°C and the saturated amine at 70°C. The pure 6-phenyl-3-cyclohexenylamine was obtained by hydrogenation of the nitro group at room temperature and 0.3 MPa H_2. In these hydrogenations, freshly prepared Raney Ni was much more selective and caused more rapid hydrogenation than the Raney Ni aged for 4–5 months.



4

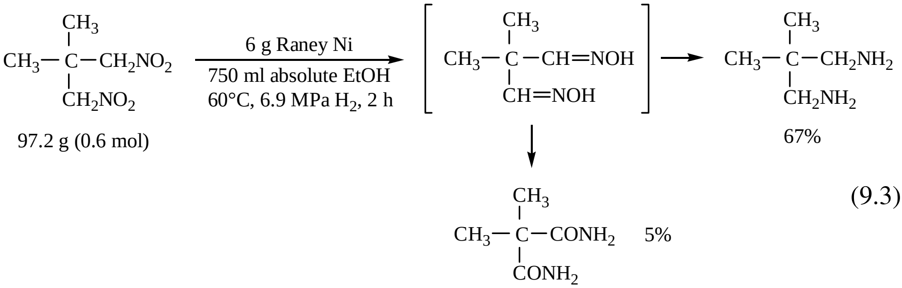


5



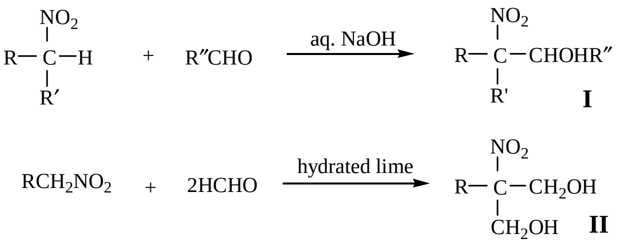
6

Rockett and Whitmore hydrogenated dinitroneopentane with Raney Ni in ethanol at 60°C and 6.9 MPa H_2 and found 67% of the expected diaminoneopentane and also 5% of the diamide of dimethylmalonic acid among the products.[9] Since aliphatic aldoximes had been known to rearrange to the corresponding amides on gentle heating over Raney Ni,[10] they suggested that the diamide was formed by the rearrangement of the intermediate dioxime in the course of the hydrogenation (eq. 9.3).

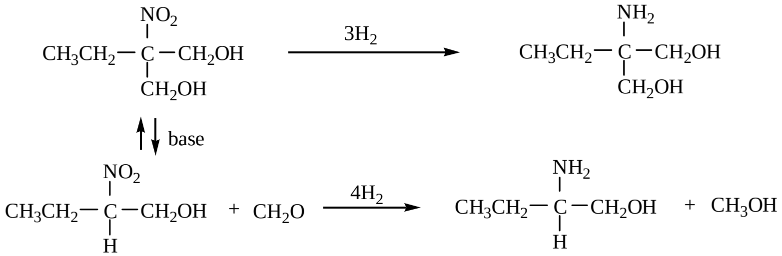


(9.3)

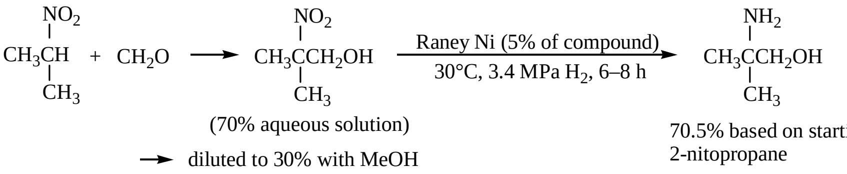
Various 2-nitro alcohols and 2-nitro 1,3-glycols of types **I** and **II**, which are readily obtained by condensation of nitroalkanes with aldehydes in the presence of base (Scheme 9.1),[11] have been hydrogenated to the corresponding amino alcohols and glycols in 70–99% yields over Raney Ni in aqueous methanol or methanol at room temperature and hydrogen pressures that varied with the substrates from 3.4 to 13.8 MPa.[12] The reaction heat evolved was sufficient to raise the temperature to 40 or 50°C. A typical run with 2-nitro-2-methyl-1-propanol is shown in eq. 9.4. Occasionally some ammonia and lower amines and amino alcohols were formed. In the case of 2-ethyl-2-nitro-1,3-propanediol, 2-amino-1-butanol was a byproduct. Since the nitro glycols are not stable in the presence of alkali, it has been suggested that the amines formed during the hydrogenation may be basic enough to cause the decomposition of unreacted nitro glycol, as illustrated in Scheme 9.2.[12]



Scheme 9.1 Condensation of nitroalkanes with aldehydes to give nitro alcohols and nitro glycols.

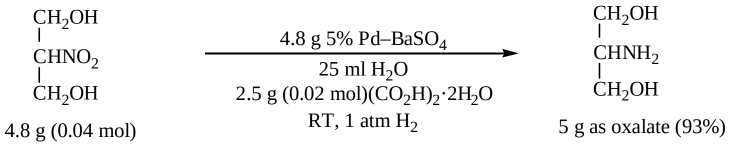


Scheme 9.2 Formation of 2-amino-1-butanol in the hydrogenation of 2-ethyl-2-nitro-1,3-propanediol over Raney Ni.



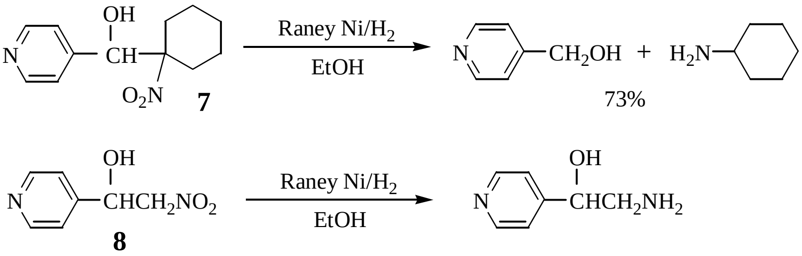
(9.4)

Schmidt and Wilkendorf hydrogenated 2-nitro-1,3-propanediol over Pd–$BaSO_4$ in aqueous solution with addition of an equivalent amount of oxalic acid that accelerated the reaction greatly, and the 2-amino glycol was obtained in 93% yield (eq. 9.5).[13] However, in the cases of nitromethane and the nitro alcohols carrying the nitro group at a primary carbon, hydrogenation under similar conditions did not proceed to give the amines and afforded the hydroxylamines or a mixture of the hydroxylamines and the amines.[14]



(9.5)

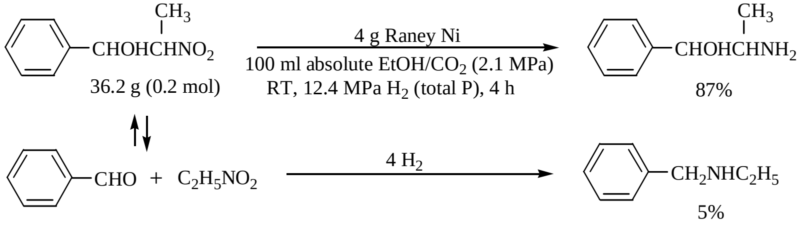
The decomposition or retro aldol condensation of 2-nitro alcohols, as described in Scheme 9.2, has often been observed in the hydrogenation over Raney Ni in neutral or basic medium. The hydrogenation of (1-nitro-1-cyclohexyl)(4-pyridyl)methanol (**7**) over Raney Ni in ethanol gave a mixture of 4-hydroxymethylpyridine and cyclohexylamine in 73% yield, although 2-nitro-1-(4-pyridyl)ethanol (**8**) gave the undecomposed amino alcohol in 70% yield (Scheme 9.3).[15] The presence of carbon dioxide[16–18] or an aliphatic acid[17,19,20] has been found to be effective for depressing the decomposition of 2-nitro alcohols as described in Schemes 9.2 and 9.3. Gakenheimer and Hartung hydrogenated a series of 2-nitro-1-alkanols of general structure $RCHOHCH(NO_2)R'$, consisting of seven to nine carbon atoms, over Raney Ni in acetic acid or in the presence of carbon dioxide in ethanol at room temperature and hydrogen pressure greater than 4.1 MPa.[17] The corresponding amino alcohols were obtained in 66–69% yields in acetic acid and in 38–54% yields in the presence of carbon dioxide. The hydrogenation was unsuccessful with palladium catalyst, and, over



Scheme 9.3 Hydrogenation and decomposition of 2-nitro-1-(4-pyridyl)alkanols.

Raney Ni in a neutral medium, no trace of the desired amino alcohol could be isolated and most of the nitrogen could be accounted for in the form of primary and secondary amines with smaller alkyl groups, as might be formed by the following reaction: $RCHOHCH(NO_2)R' \rightarrow R'CH_2NH_2 + RCH_2NHCH_2R'$. The decomposition was suggested to occur at a partially hydrogenated product, since the nitro alcohol remained unaffected after 72 h at room temperature in the presence of the corresponding amino alcohol, hydrogen chloride, sodium hydroxide, or Raney Ni. The amino alcohol was not decomposed over Raney Ni at temperatures as high as 85°C and pressures as high as 2.1 MPa H_2.

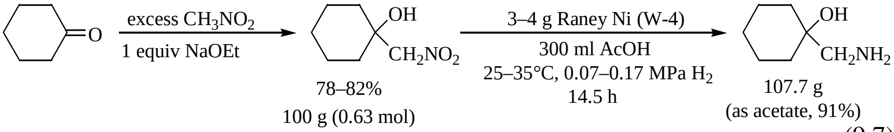
Hoover and Hass hydrogenated 2-nitro-1-phenyl-1-propanol over Raney Ni in ethanol in the presence of sufficient carbon dioxide to produce a pressure of 2.1 MPa and obtained the corresponding amino alcohol (a mixture of *dl*-norephedrine and *dl*-norisoephedrine) in 87% yield.[18] The formation of *N*-ethylbenzylamine, a byproduct, was depressed to 5% under these conditions (eq. 9.6). Without carbon dioxide the yield of *N*-ethylbenzylamine was approximately 45%.



(9.6)

Dauben, Jr. et al. obtained 1-(aminomethyl)cyclohexanol in 91% yield by hydrogenating 1-(nitromethyl)cyclohexanol over Raney Ni in acetic acid at 25–35°C and 0.07–0.17 MPa H_2 (eq. 9.7).[20] The reaction temperature was carefully controlled not to exceed 35°C by rapid circulation of cooling water during the first 30–60 min. Comparable yields (86–87%) were obtained in larger runs (350 g) or by hydrogenation in 15% acetic acid–85% ethanol, although the rate decreased to about one-half in the diluted solvent. The condensation of cyclohexanone with nitromethane was also improved to give 78–82% yield of 1-(nitromethyl)cyclohexanol with use of a molar equivalent of condensing agent, ethanolic sodium ethoxide, and excess nitromethane

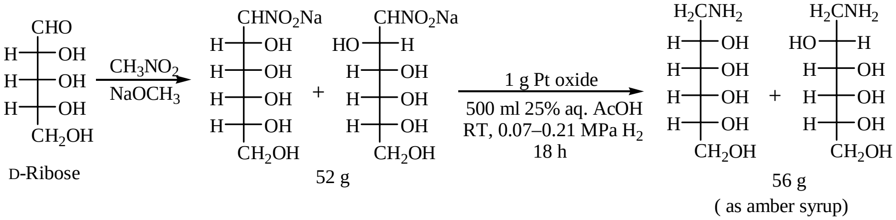
(see eq. 9.7). Thus, 1-(aminomethyl)cyclohexanol was obtained in 68–75% overall yield from starting cyclohexanone.



(9.7)

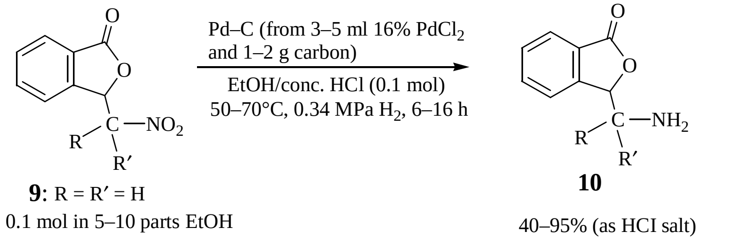
Hydrogenation of the nitro alcohol over Raney Ni in methanol at 80°C and hydrogen pressures ranging from 0.30 to 21 MPa was quite unsatisfactory. A mixture of high-boiling amines, presumed principally as bis(cyclohexanemethyl)amine and cyclohexanol, as well as methylamine and ammonia, was found in the product.[21] Low-pressure hydrogenation of the nitro alcohol at room temperature in ethanol over Raney Ni or platinum oxide also gave only low yields (<35%) of the amino alcohol.[20]

The catalytic hydrogenation of nitro alcohol to amino alcohol has been applied to the synthesis of an intermediate leading to sugar alcohols. The condensation of nitromethane with pentoses in the presence of sodium methoxide, followed by hydrogenation over platinum oxide and deamination with nitric acid, gave the alditols with one more carbon atom.[22] The reaction sequence is as follows: pentose → 2-epimeric sodio *aci*-nitro alcohols → 2-epimeric hexitylamines → 2-epimeric hexitols + 2-epimeric 1,4-anhydrohexitols. The 2-epimeric sodio *aci*-nitro alcohols were hydrogenated to 2-epimeric hexitylamines over platinum oxide in acetic acid. An example is shown in eq. 9.8 with D-ribose.



(9.8)

3-Phthalidylnitromethane (**9**) and its alkyl- and dialkyl-substituted derivatives (R = H, Me; R′ = H, C_1–C_4 alkyl) were hydrogenated to the corresponding amino compounds (**10**) in 45–95% yields (as hydrochlorides) over in situ–prepared Pd–C catalyst in an alcoholic solvent in the presence of an equivalent amount of hydrochloric acid, mostly at 50–70°C, and an initial hydrogen pressure of 0.34 MPa (eq. 9.9).[23,24] Over platinum oxide in acetic acid the hydrogenation of **9** (R = R′ = H) proceeded beyond the stage of phthalidylmethylamine, although the amine could be isolated in 48% yield as hydrochloride when the reaction was interrupted as soon as 3 equiv of hydrogen had been consumed. Prolonged hydrogenation absorbed 7 equiv of hydrogen and on heating the product to 130–140°C, followed by vacuum sublimation, octahydroisocarbostyril (**11**) was obtained in 57.5% yield (eq. 9.10).[25]



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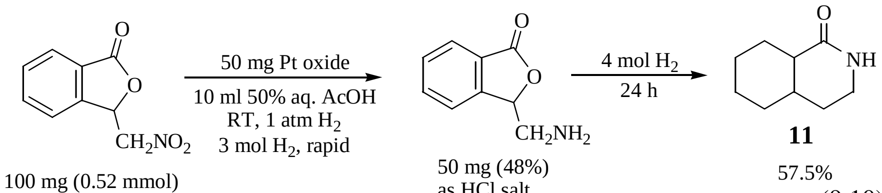
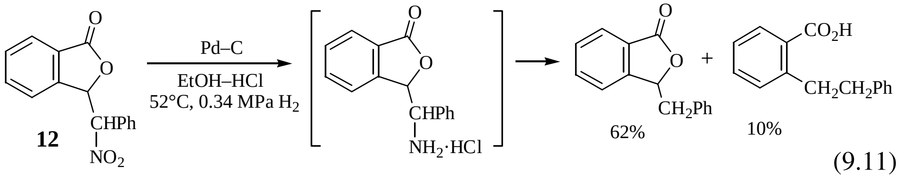


(9.10)

Hydrogenation of phenylphthalidylnitromethane (**12**) over Pd–C in acid solution gave nonbasic products as the result of hydrogenolysis at the benzyl–nitrogen and the benzyl–oxygen bonds (eq. 9.11). Phenylphthalidylmethylamine was obtained, although in only 19% yield, in hydrogenation over 9% Pd–ZrO_2 in ethanol at 52°C and 0.33 MPa H_2.[24]

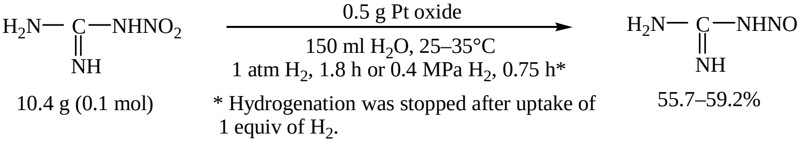


(9.11)

9.2.3 Hydrogenation to Nitroso or Hydroxyimino and Hydroxyamino Compounds

Examples of the hydrogenation of nitroalkanes to nitroso or hydroxylimio compounds are rather few. On the other hand, more examples are known for the hydrogenation of nitroalkanes to the corresponding hydroxylamines.

Nitroguanidine was hydrogenated to nitrosoguanidine in yields of 56–59% over platinum oxide and in 37–44% yields over Raney Ni.[26] Water was found to be most suitable as the reaction medium for the platinum catalyst (eq. 9.12). Over Raney Ni, somewhat greater rates and yields were obtained in methanol than in water.



(9.12)

Hydrogenation of nitroguanidine to aminoguadinine was successful (a 68.3% yield as sulfate) over platinum oxide in 15% aqueous acetic acid (~1.6 molar ratio of acid to nitroguanidine) at room temperature and 12.5 MPa H_2.[27] Hydrogenation over Raney Ni in methanol at room temperature and 12.5 MPa H_2 gave a lower yield (55.2% as carbonate). The yield of aminoguanidine fell off with increasing temperatures to 125°C, more rapidly with Raney Ni than with platinum oxide. In one patent, nitroguanidine was hydrogenated over Raney Ni in an aqueous suspension at pH 5 at room temperature and 10 MPa of 85:15 hydrogen–nitrogen mixture.[28]

Nitromethane and nitro alcohols with a primary nitro group were hydrogenated to the corresponding hydroxylamines in 69–98% yields over Pd–$BaSO_4$ in the presence of oxalic or acetic acid in aqueous or alcoholic solution, although 2-nitro-1,3-propanediol, with a secondary nitro group, gave the corresponding amine under the same conditions (see eq. 9.5).[14] Thus, nitromethane (eq. 9.13), 2-nitroethanol, and 1-nitro-2-propanol were hydrogenated in aqueous oxalic acid solution to give the corresponding hydroxylamine oxalates in high yields. 1-Nitro-2-butanol and 1-nitro-2-pentanol (eq. 9.14) were hydrogenated in 96% ethanol solution in the presence of oxalic acid to give the corresponding hydroxylamine oxalates in yields of 79 and 81%, respectively. 5-Nitro-2-methyl-4-pentanol was hydrogenated in 96% alcohol in the presence of acetic acid to give the hydroxylamine in 69% yield (isolated as oxalate).

$$\underset{6.1\text{ g }(0.1\text{ mol})}{CH_3NO_2} \xrightarrow[\substack{77\text{ ml }H_2O/6.3\text{ g }(0.05\text{ mol})\text{ crystalline oxalic acid}\\ \text{RT, 1 atm }H_2\text{, ~3 h}}]{1\text{ g }5\%\text{ Pd–}BaSO_4} \underset{9\text{ g }(98\%)}{CH_3NHOH\cdot \tfrac{1}{2}\,H_2C_2O_4} \qquad (9.13)$$

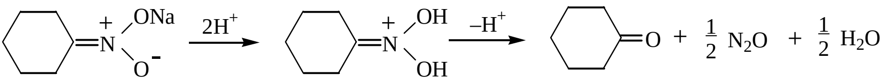
$$\underset{6.6\text{ g }(0.05\text{ mol})}{CH_3CH_2CH_2CH(OH)CH_2NO_2} \xrightarrow[\substack{25\text{ ml }96\%\text{ EtOH}\\ 3.15\text{ g }(0.025\text{ mol})\text{ cryst. oxalic acid}\\ \text{RT, 1 atm }H_2\text{, ~ 1.5 h}}]{1.5\text{ g }5\%\text{ Pd–}BaSO_4} \underset{6.6\text{ g }(81\%)}{CH_3CH_2CH_2CH(OH)CH_2NHOH\cdot \tfrac{1}{2}\,H_2C_2O_4} \qquad (9.14)$$

4-Nitro-2-methyl-3-butanol and 1-nitro-2-octanol were hydrogenated in aqueous ethanol solution in the presence of oxalic acid and acetic acid, respectively, to give 76 and 69.5% yields of the hydroxylamine oxalates. In one patent, nitromethane (684 g, 11.2 mol) was hydrogenated over 2 g of 5% Pd–C in 60% aqueous H_2SO_4 (1010 g, 6.18 mol)–toluene (684 g), as a water-immiscible solvent, at 50°C and 4.1 MPa H_2 and a 92% of *N*-methylhydroxylamine sulfate was obtained from the aqueous phase together with 6% of methylamine sulfate.[29]

Nitrocyclohexane can be converted to cyclohexanone oxime, a precursor to ε-caprolactam, either directly by hydrogenation to the oxime or by hydrogenation to cyclohexylhydroxylamine followed by oxidation to the oxime. Since the hydrogenation of nitrocyclohexane may thus be an important step for a commercial production of ε-caprolactam from cyclohexane, numerous articles and patents on this hydrogenation have been described in the literature. Grundmann surveyed a number of nickel- and copper-based catalysts for the selective hydrogenation of nitrocyclohexane to cyclohexanone oxime, with the results that none of them were effective for the hydrogena-

tion. However, silver-based catalysts, in particular, those containing zinc and chromium, were found to give good yields of the oxime. Thus, cyclohexanone oxime was obtained in 60–70% yields in the hydrogenation of nitrocyclohexane over Ag–Zn–Cr oxide in methanol at 90–105°C and 5–15 MPa H_2.[30] An effective catalyst, Ag–Zn–Cr oxide stabilized with CaO, was prepared from 3.4 g $AgNO_3$, 4.7 g $Ca(NO_3)_2{\cdot}4H_2O$, 47 g $Zn(NO_3)_2{\cdot}6H_2O$, and 25.2 g $(NH_4)_2Cr_2O_7$. Some of other effective catalyst systems for the hydrogenation to cyclohexanone oxime (yields in parentheses) are as follows: a platinum catalyst, prepared by adding an aqueous solution of 24 g $Zn(NO_3)_2{\cdot}6H_2O$, 2.4 g $Ca(NO_3)_2{\cdot}4H_2O$ and 5 g $H_2PtCl_6{\cdot}6H_2O$ to a solution of 12.6 g of $(NH_4)_2Cr_2O_7$ and 25 ml of concentrated ammonia, in methanol at 105°C and 10 MPa H_2 (65% yield);[31] 5% Pd–C in methanol-hydrochloric acid at 24–30°C and 3 MPa H_2 (> 86% yield);[32] a Ag–Zn–Cr–Ca–SiO_2 catalyst in a gaseous mixture of 4% nitrocyclohexane, 28% methanol, and 68% hydrogen at 110°C and atmospheric pressure (98% based on nitrocyclohexane converted);[33] and lead-poisoned Pd–acetylene black (5:100) in water at 160°C and 3.4 MPa H_2 (79.2% yield).[34] Guyer and Merz obtained over 70% yield of cyclohexanone oxime in 90% conversion by adding continuously a methanolic solution of the sodium salt of nitrocyclohexane to a Pt–C suspension in methanolic hydrogen chloride at 20 MPa H_2.[35] By keeping the concentration of *aci* form of nitrocyclohexane always to a low level in this manner, the formation of cyclohexanone by the Nef reaction (see Scheme 9.4) could be depressed to ~5%. The following are examples of the catalyst systems for the hydrogenation of nitrocyclohexane to the hydroxylamine: over 1% Pd–$CaCO_3$ in methanol at 25°C and subatmospheric pressure of hydrogen (100–200 mmHg) (75% yield);[36] over a Ag–Zn–Cr–Al–Mg oxide in ether at 125°C and 20 MPa H_2 to give a mixture of 263 parts of hydroxylamine, 19.5 parts of oxime, 18 parts of amine, and 20 parts of unreacted nitrocyclohexane;[37] over a Ag–Mn–Cr oxide in ethanol at 80°C and 10 MPa H_2 (97% yield based on nitocyclohexane converted);[38] over a 5% Pd–Al_2O_3 in water containing an equivalent amount of acetic acid at 0.1–0.5 MPa H_2;[39] in a continuous process by passing 27 g nitrocyclohexane and 0.7 g cyclohexylamine in 250 ml cyclohexane through a 50-g bed of 8 mesh 0.5 wt% Pd–Al_2O_3 at temperatures below 40°C and approximately 1 atm H_2 and recycling the filtrate after separating the hydroxylamine by cooling to 5°C (95% yield).[40]

Meister has shown that the product selectivity in the formation of cyclohexanone oxime and cyclohexylhydroxylamine over a Ag–Zn–Cr oxide catalyst depended greatly on the reaction temperature as seen from the results in Table 9.2.[41] The proportion of cyclohexanone oxime in the product increased with increasing temperature while lower temperature and high hydrogen pressure favored the formation of cyclohexylhydroxylamine. These results, together with the facts that cyclohexanone oxime was not hydrogenated over Pd–$CaCO_3$ under conditions that allowed the hydrogena-



Scheme 9.4 Formation of cyclohexanone from *aci*-nitrocyclohexane by the Nef reaction.

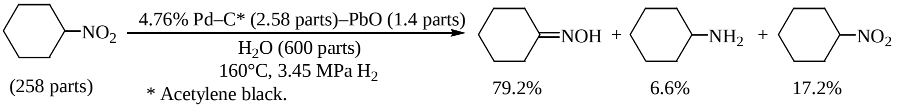
TABLE 9.2 The Effect of Temperature on Hydrogenation of Nitrocyclohexane over Silver–Zinc–Chromium Oxide[a]

Temperature (°C)	H_2 pressure (MPa)	Proportion of Product (%) Cyclohexanone Oxime	Cyclohexylhydroxylamine
45	20	11.9	56
65	20	41.6	23.5
95	5.0	63.8	11.3
105	2.5	72.4	0

[a]Data of Meister, H. *Justus Liebigs Ann. Chem.* **1964**, *679*, 83. Reprinted with permission from Wiley-VCH, Weinheim.

tion of nitrocyclohexane and cyclohexylhydroxylamine to give cyclohexylamine, indicate that nitrocyclohexane is hydrogenated to cyclohexylamine not through the oxime but through nitrosocyclohexane and cyclohexylhydroxylamine as intermediates.[35,41] At higher temperatures the formation of cyclohexanone oxime tends to increase by rearrangement of nitrosocyclohexane or its dimer. Dimeric nitrosocyclohexane was hydrogenated to azoxycyclohexane almost exclusively in neutral solvent at 20°C, but, at 40°C, ~60% was hydrogenated to cyclohexylamine. In acetic acid, dimeric nitrosocyclohexane as well as azoxycyclohexane were hydrogenated to hydrazocyclohexane. From these results it is deduced that dimeric nitrosocyclohexane is hydrogenated to azoxy- or hydrazocyclohexane and at an elevated temperature monomeric nitrosocyclohexane formed by dissociation is hydrogenated to cyclohexylamine.

Meister also studied the hydrogenation of nitrocyclododecane and related products in detail.[41] In general, the behavior of nitrocyclododecane toward hydrogenation was quite similar to that of nitrocyclohexane except that the hydrogenation proceeds more slowly and a very pure material is needed. Since azoxycyclohexane is formed more readily than azoxycyclododecane—which may be related to a higher stability of dimeric nitrosocyclohexane versus dimeric nitrosocyclododecane—the hydroxylamine may be obtained in higher yield in the hydrogenation of nitrocyclododecane than in nitrocyclohexane (cf. eq. 9.16 with eq. 9.17). Cyclododecanone oxime, which was not hydrogenated over Pd–$CaCO_3$ under mild conditions, could be hydrogenated to cyclododecylamine almost quantitatively over Raney Ni at temperatures of 80°C or higher and high hydrogen pressures. Using the results described above, the reactions for the hydrogenation of nitrocycloalkanes can be formulated as shown in Scheme 9.5. Typical examples of respective hydrogenation are shown in eqs. 9.15–9.24 with nitrocyclohexane and/or nitrocyclododecane series.[34,36,41]



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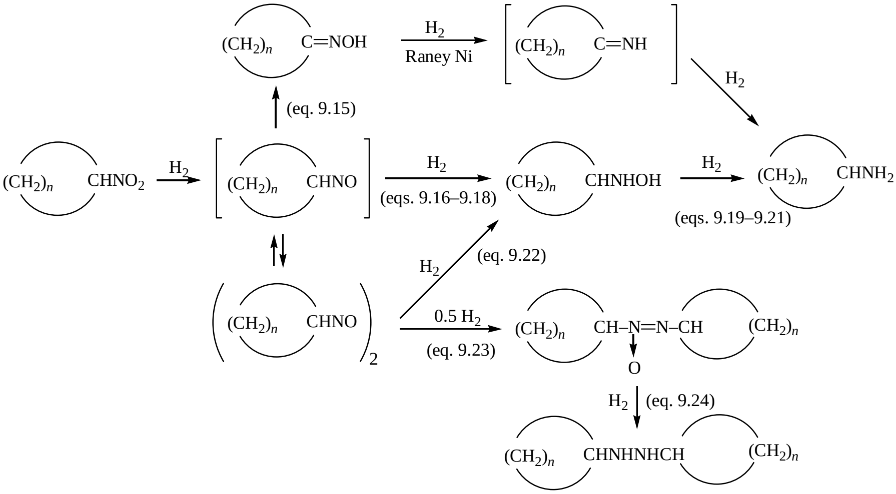
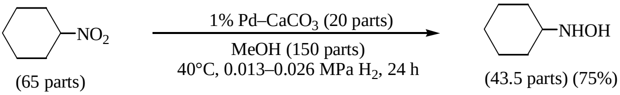


Scheme 9.5 Hydrogenation pathways of nitrocycloalkane (the uptake of hydrogen is based on monomeric compound).



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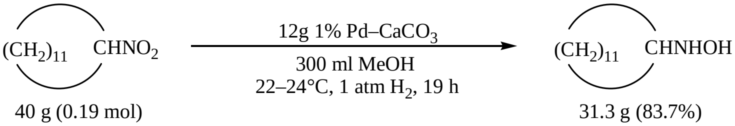

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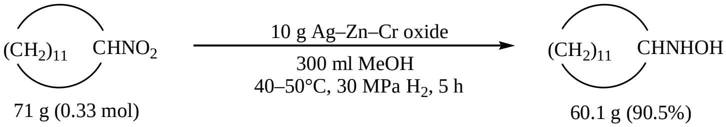

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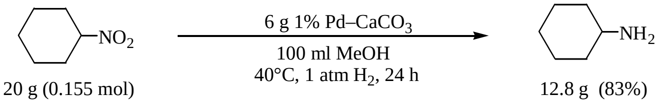

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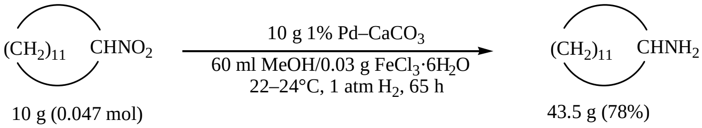

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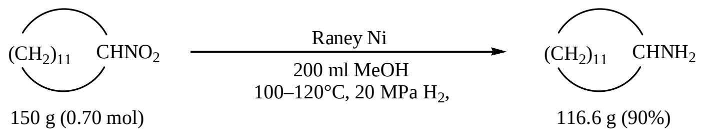

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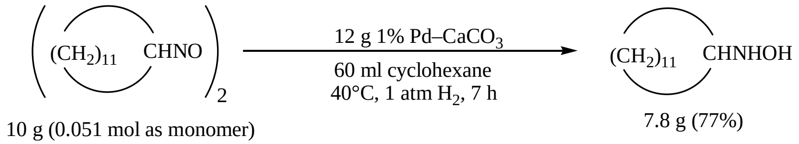

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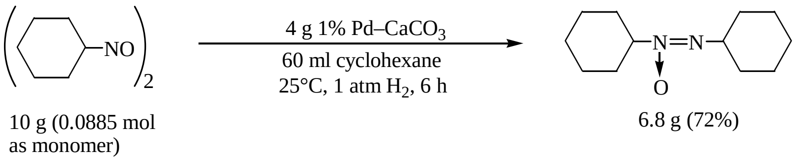

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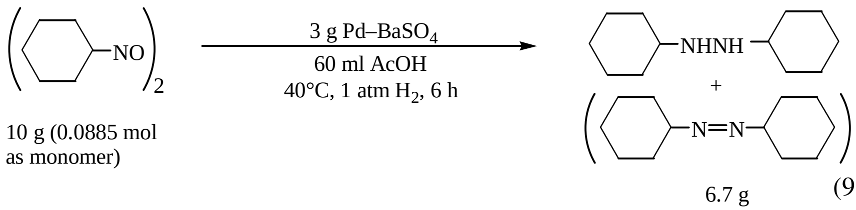
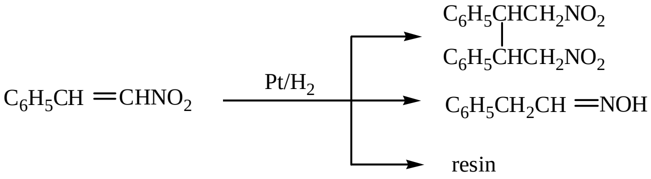


(9.24)

9.2.4 Conjugated Nitroalkenes

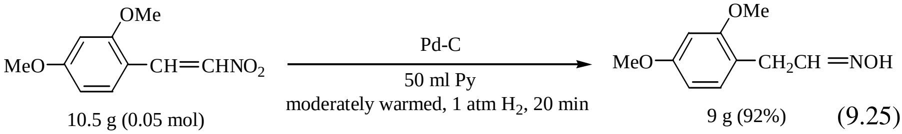
Smith and Bedoit, Jr. have shown that, in contrast to the cases for nitroalkanes, the rates of hydrogenation of 2-nitro-1-butene and β-nitrostyrene over platinum oxide in acetic acid are zero-order with respect to the substrate and first-order with respect to hydrogen pressure. Thus, α,β-unsaturated nitroalkenes behave similarly to aromatic nitro compounds and are hydrogenated rapidly until 1.5–2 mol of hydrogen has been absorbed.[1] Over Raney Ni β-nitrostyrene was not appreciably hydrogenated at room temperature and low hydrogen pressures, and 2-nitro-1-butene underwent hydrogenation to the extent of about 10% of theoretical. The rapid decrease in the rate of hydrogenation with the latter compound was attributed to the formation of polynitrobutene, which was the major product of the hydrogenation. When 2-nitro-1-butene was hydrogenated over platinum oxide in acetic acid at 0.41 MPa H_2, 2 mol of hydrogen was absorbed rapidly and the product was confirmed to be 2-butanone oxime, although the faint order of an amine was found to be present when the solution was made alkaline.[42] The products of the hydrogenation of β-nitrostyrene are rather complex. Sonn and Schellenberg isolated a dimeric product, 1,4-dinitro-2,3-diphenylbutane, from the product of the hydrogenation over platinum black (Willstätter) in ethanol.[43] In acetic acid, the hydrogenation proceeded more rapidly and ~1.7 mol of hydrogen was absorbed in 4 h. Besides a lesser amount of the dinitrodiphenylbutane than obtained in ethanol, phenylacetaldehyde oxime was isolated together with unidentified resinous material.[43] Smith and Bedoit, Jr. obtained practically the same results and suggested



Scheme 9.6 Hydrogenation products of β-nitrostyrene over platinum catalyst.

that these products were formed simultaneously, as shown in Scheme 9.6. The hydrogenations of the nitro group and of the C–C double bond was considered to take place simultaneously, since the saturated product of a nitroalkane type should be much less reactive and could not be an intermediate for the formation of the oxime.[44]

Hydrogenation of β-nitrostyrene over colloidal palladium (Paal) as catalyst gave generally the same results as with platinum catalyst.[43] The hydrogenation of β-methyl-β-nitrostyrene (200 parts) over 5% Pd–C (2 parts) in water (600 parts) at 31–35°C and 3.4 MPa H_2 gave 63% of 2-nitro-1-phenylpropane, 17.3% of 1-phenyl-2-propanone oxime and 4.9% of 1-phenyl-2-propanone.[45] Reichert and Koch obtained the oximes of substituted phenylacetaldehydes in high yields by hydrogenation of the β-nitrostyrenes, prepared by the reaction of *o*-and *p*-methoxybenzaldehydes, 2,4- and 3,4-dimethoxybenzaldehydes , and piperonal with nitromethane, over Pd–C in pyridine.[46] For example, the hydrogenation of 2,4-dimethoxy-β-nitrostyrene over Pd–C in pyridine gave a 92% yield of the corresponding phenylacetaldehyde oxime (eq. 9.25). Similarly, an 85% of dioxime was obtained in the hydrogenation of 2,4-bis(β-nitrovinyl)anisole.[47]



(9.25)

Seifert and Condit obtained high yields of oximes in the hydrogenation of 1-nitrocyclooctene and 1-nitro-1-octadecene over Pd–C in methanol containing 0.5–1.0 equiv of hydrogen chloride (Table 9.3).[48] With pyridine as solvent, the rate of hydrogenation was significantly lower than in acidic methanol. Lower yields of the oximes in pyridine were explained by the loss of substrate that might result from an addition of the piperidine produced by the hydrogenation of pyridine during the reaction. In methanol containing small amounts of pyridine, the rate of hydrogenation decreased sharply after 1 mol of hydrogen had been absorbed and the nitroalkanes were the major products. Three possible routes for the formation of cyclooctanone in methanolic hydrogen chloride have been discussed by Seifelt and Condit: (1) hydrolysis of the oxime, (2) hydrogenation of some oxime to the imine and subsequent hydrolysis, and (3) formation of *aci* form of nitrocyclooctane formed by 1,4-addition of hydrogen and subsequent Nef decomposition to give cyclooctanone and nitrous oxide (see Scheme 9.4). The first possibility was excluded since cycooctanone oxime was not hydrolyzed under the reaction

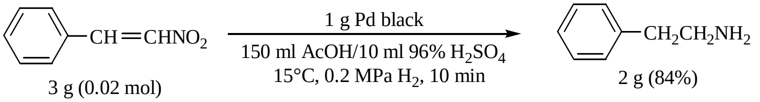
TABLE 9.3 Selective Hydrogenation of 1-Nitrocyclooctene (I) and 1-Nitro-1-octadecene(II) over Pd–C[a,b]

Nitro-alkene	Solvent	HCl/ Nitroalkene (mol/mol)	H_2 Uptake (mol/mol)[c]	Wt% Pyridine in Methanol	Mol% Composition of Crude Products		
					Oxime	Nitroalkane	Carbonyl Compound
I	MeOH	1	2.1	—	83	0	17[d]
II	MeOH	0.5	1.8	—	73	2	13[e]
I	Pyridine	—	2.5	—	60	3	Trace[d]
II	Pyridine	—	1.9	—	60	—	—
I	MeOH	—	1.0	1.3	Trace	83	10[d]
II	MeOH	—	1.1	2.0	Trace	50	10[e]

[a]Data of Seifelt, W. K.; Condit, P. C. *J. Org. Chem.* **1963**, *28*, 265. Reprinted with permission from American Chemical Society.
[b]The hydrogenations were carried out on a 2–50 mmol scale over 5% Pd–C (1.3–4 wt% Pd metal) at room temperature and 0.069–0.41 MPa H_2.
[c]Corrected for hydrogenation of pyridine that was determined separately.
[d]Cyclooctanone.
[e]The values were estimated and based on the assumption that the carbonyl compound was stearaldehyde.

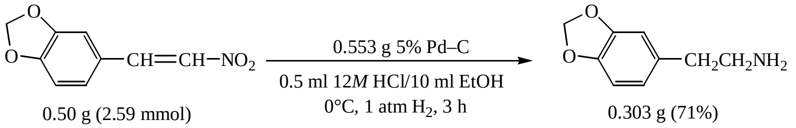
conditions. It has been suggested that the ketone might be formed through the second route since further hydrogenation of the oxime was found to occur to some extent, although the Nef reaction was not investigated.

The hydrogenation of β-nitrostyrenes to β-phenethylamines can be accomplished over palladium catalyst in strongly acidic conditions.[49–51] Kindler et al. hydrogenated β-nitrostyrene to 2-phenethylamine in 84% yield over a palladium black in acetic acid–sulfuric acid (eq. 9.26).[49] In the absence of sulfuric acid the uptake of the same amount of hydrogen required a much longer time and the phenethylamine was obtained in only slight amounts.



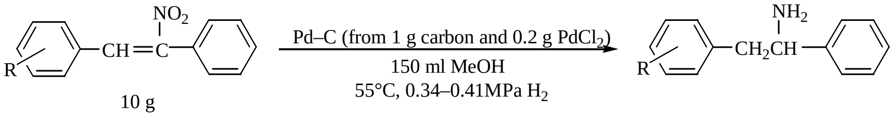
(9.26)

Reichert and Koch converted β-nitrostyrenes into 2-phenethylamines in two steps: first hydrogenated to the oximes over Pd–C in pyridine, followed by hydrogenation of the oximes to the phenethylamines over platinum oxide in ethanol in the presence of oxalic acid.[46] Kohno et al. recommend the hydrogenation of β-nitrostyrenes over Pd–C in EtOH-HCl.[52] Under these conditions, the corresponding phenethylamines were obtained in 65–99% isolated yields of pure amines or amine hydrochlorides. The hydrogenations of 3,4-methylenedioxy- (eq. 9.27), 4-hydroxy-3-methoxy-, and 3-hydroxy-4-methoxy-β-nitrostyrenes gave higher yields of the corresponding phenethylamines at 0°C than at room temperature. 3,4-Bis(benzyloxy)- and 4-benzyloxy-β-nitrostyrenes afforded the corresponding hydroxyphenethylamine hydrochlorides in 99 and 94% yields, respectively.



(9.27)

Substituted α-nitrostilbenes were hydrogenated to 1,2-diphenylethylamines in 52–87% yields, conveniently in methanol over in situ–prepared Pd–C catalyst (eq. 9.28).[53] In these cases the hydrogenation was carried out in presence of the hydrogen chloride formed from palladium chloride, the amount of which, however, was much smaller (~0.0022 mol) for the nitrostilbenes hydrogenated (0.037–0.042 mol). In one instance, α-nitro-4′-methoxystilbene gave rise to a small amount of the corresponding oxime when the hydrogen uptake was less than theoretical.

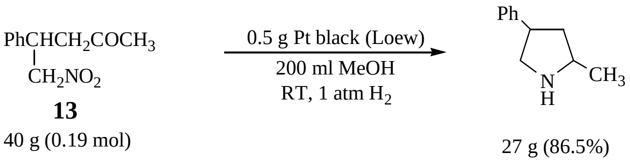


R	Time (h)	Yield (%) (as HCl salt)
2-MeO	16	52
2-HO	3	86
4-MeO	3	67
4-HO	3	75
3-MeO-4-HO	1	87

(9.28)

9.2.5 Hydrogenation Accompanied by Cyclization

γ-Nitro ketones may be hydrogenated to give cyclized products resulting from an intramolecular condensation. Kohler and Drake obtained a pyrrolidine derivative in 86.5% yield by hydrogenation of γ-nitro methyl ketone **13** over a platinum black in methanol (eq. 9.29).[54] The hydrogenation of γ-nitro phenyl ketones, however, gave only small amounts of pyrrolidine derivatives under the same conditions. When the hydrogenation of the nitro ketone **14** was interrupted with uptake of 2 equiv of hydrogen, the solution contained unchanged nitro ketone, the amino ketone, hydroxypyrroline **15a** or **15b**, and the pyrrolidine derivative. Since the amino ketone was stable in neutral and alkaline solutions and the pyrroline was always present in the solution after the cease of hydrogen absorption, it was suggested that these products could not be the intermediates for the pyrrolidine derivative.



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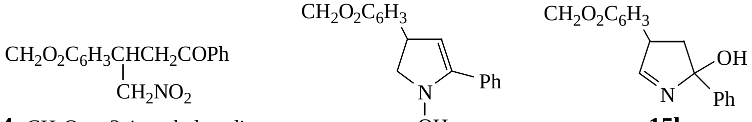
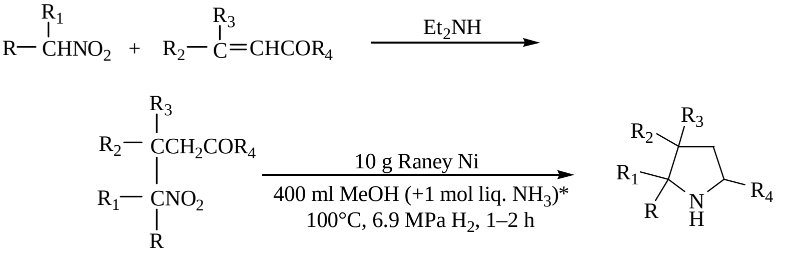


14: CH_2O_2 = 3,4-methylenedioxy **15a** **15b**

Kloetzel prepared various γ-nitro ketones by a Michael-type condensation of nitroalkanes with α,β-unsaturated ketones in the presence of diethylamine, and hydrogenated the γ-nitro ketones thus obtained to the corresponding pyrrolidines in 51.5–94% yields over Raney Ni in methanol at 100°C and 6.9 MPa H_2 in both the presence and absence of ammonia (eq. 9.30).[55] It is noted that the hydrogenation of γ-nitro phenyl ketones (R_4 = Ph, eq. 9.30) over Raney Ni in the presence of ammonia yielded high yields of the corresponding pyrrolidines, which were obtained in only small quantities with use of platinum under the conditions of eq. 9.29.



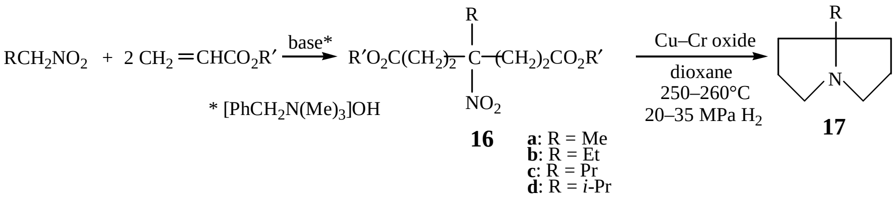
(9.30)

0.33–0.5 mol

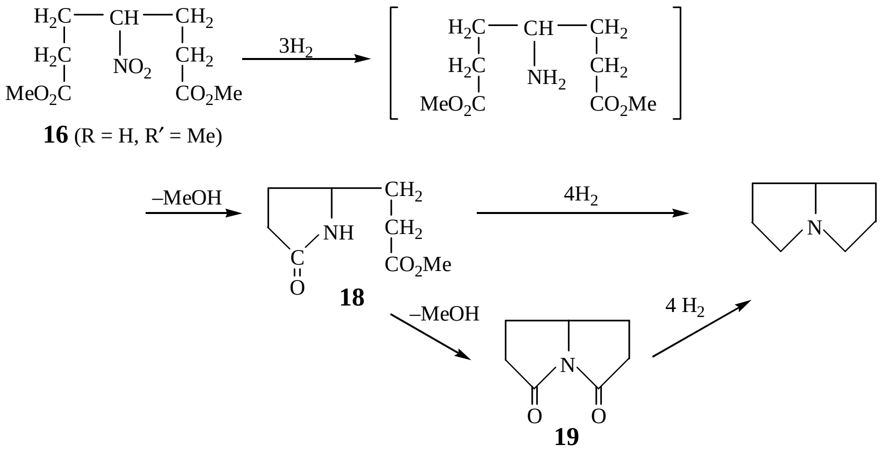
	Yield (%)
R = R_1 = R_3 = H; R_2 = R_4 = Ph	82*
R = Et; R_1 = R_3 = H; R_2 = Ph; R_4 = Me	78; 60*
R = R_1 = Me; R_2 = R_4 = Ph; R_3 = H	94; 87*
R = Et; R_1 = R_3 = H; R_2 = R_4 = Ph	72; 77*

* Hydrogenated in the presence of NH_3.

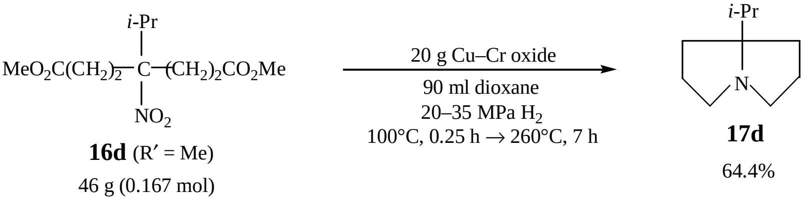
γ-Nitro diesters **16a–16d**, prepared by condensation of 1-nitroalkanes with 2 mol of acrylates, were hydrogenated to give 8-alkylpyrrolizidines **17a–17d** (in 60–65% yields for **17b–17d**) over copper–chromium oxide at 250–260°C and 20–35 MPa H_2 (Scheme 9.7).[56,57] First the temperature was kept at 125°C until sufficient hydrogen had been absorbed to reduce the nitro group and was then raised and maintained at 250–260°C. The use of dioxane as solvent was found to be advantageous, since the reaction time in dioxane was one-third that required in ethanol. A typical example is shown in eq. 9.31.[57]



Scheme 9.7 Synthesis and hydrogenation of γ-alkyl-γ-nitropimelates leading to 8-alkylpyrrolizidines.



Scheme 9.8 The hydrogenation pathway of dimethyl γ-nitropimelate leading to pyrrolizidine.



(9.31)

The lactams, which may be formed from the intermediate amino diesters, should be the intermediates leading to the pyrrolizidines. The lactam **18** was isolated on distillation of the product of hydrogenation of dimethyl γ-nitropimelate (**16**: R = H, R′ = Me) over platinum oxide in methanol at 25°C and 0.2–0.3 MPa H_2. When the lactam **18** was subjected to treatment with hydrogen at 250°C and 30 MPa H_2 over copper–chromium oxide, no absorption of hydrogen was observed, and an intermediate that was in excellent agreement with the empirical formula of 3,5-dioxopyrrolizidine (**19**) was obtained. Thus, the hydrogenation pathway of dimethyl γ-nitropimelate leading to the formation of pyrrolizidine is presumed to involve that through the formation of **19** (Scheme 9.8).[56]

9.3 AROMATIC NITRO COMPOUNDS

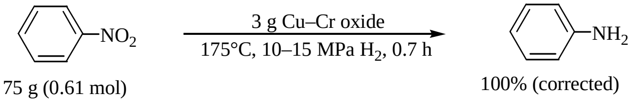
9.3.1 Hydrogenation to Amines

The nitro group attached to an aromatic ring is one of the most reactive functions toward both chemical and catalytic reductions and in most cases preferentially hydrogenated over other reducible functions. Hydrogenation of aromatic nitro compounds

has been performed over a variety of catalysts, not only over the transition metals but also over their oxides and sulfides in either vapor phase or liquid phase at low or high pressures. The hydrogenation is highly exothermic. For example, the heat of hydrogenation of nitrobenzene to aniline is as great as 493 kJ (118 kcal)·mol^{-1}. Accordingly, care must be taken to prevent the reaction from becoming too violent. This can be done by controlling the scale of reaction, the catalyst to substrate ratio, the reaction temperature and pressure, and use of solvent, as well as an efficient device for removing the reaction heat.

The vapor-phase hydrogenation of nitrobenzene to aniline was first reported by Sabatier and Senderens over copper and nickel catalysts,[58,59] and a related patent was applied in 1901 with nickel, copper, cobalt, iron, and palladium catalysts.[60] The hydrogenation to aniline was performed over a nickel catalyst of limited activity at 200°C. Above this temperature or over an active catalyst, the aromatic nucleus was also hydrogenated to give cyclohexylamine. Copper was found to be superior to nickel for the production of aniline without causing the hydrogenation of the aromatic ring. The hydrogenation over copper catalyst started at 250°C and was rapid between 300 and 400°C to give almost quantitative yields of aniline. The hydrogen may be replaced by water gas. For depressing the ring hydrogenation over nickel catalyst, Yoshikawa used a nickel catalyst containing 1.5–2% of nickel sulfate.[61] A nickel catalyst poisoned with thiophene was also employed for this purpose.[62] Sweeny et al. showed that dinickel phosphide, prepared by reduction of nickel orthophosphate in hydrogen at 545°C, was an excellent catalyst for vapor-phase hydrogenation of nitrobenzene to aniline and water.[63] Yields of over 95 wt% of aniline were obtained at atmospheric pressure and 360–420°C, the feed rate of nitrobenzene, 10 mmol·h^{-1}·g^{-1} over $NiP_{0.584}$, and hydrogen:nitrobenzene molar ratio of 11:23. In contrast to nickel molybdate,[64] nickel chromate,[64] and nickel vanadate,[65] evidence was drawn to indicate that nickel phosphate was reduced to dinickel phosphide containing no metallic nickel.

The hydrogenation of aromatic nitro compounds in the liquid phase is possible over a variety of catalysts. Nickel, platinum, palladium, and copper catalysts are among those employed most frequently. Hydrogenations over copper–chromium oxide (eq. 9.32)[66] and Ni–kieselguhr (eqs. 9.33 and 9.34)[67] are carried out at elevated temperatures and pressures with or without use of solvent. Hydrogenations over Raney Ni and Urushibara Ni may be performed at high pressures (eqs. 9.35, 9.36)[68,69] as well as at low pressures but with larger amounts of catalyst than those required at high pressures (eq. 9.37).[70]



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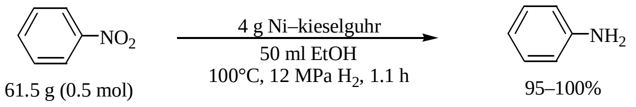

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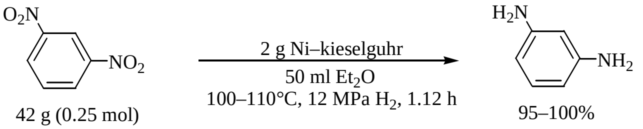

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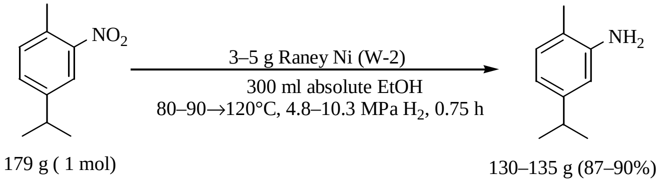

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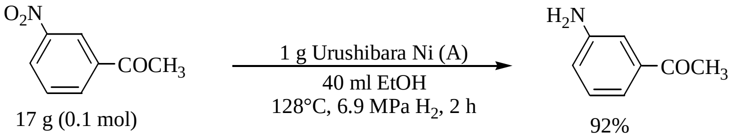

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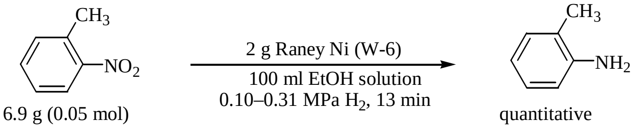


(9.37)

Debus and Jungers showed that Raney Ni was subject to serious deactivation when nitrobenzene was introduced on the catalyst.[71] The deactivation was attributed to the oxidation of the nickel catalyst caused by a notable elevation of the surface temperature. At temperatures higher than 150°C, the nickel oxide formed may be reducted to nickel and the catalytic activity may be regenerated, and therefore it is possible to transform nitrobenzene quantitatively into aniline. The hydrogenation over Raney Ni was found to be accelerated at an initial period of hydrogenation. It was confirmed that this acceleration was caused by the water formed during hydrogenation, by adding a significant amount of water prior to hydrogenation. Thus, the initial rate of hydrogenation at 30°C and 1–2 MPa H_2 was increased by a factor of 8.5 by adding 25 ml of water to a mixture of 0.5 mol (61.5 g) of nitrobenzene and 125 ml of isopropyl alcohol. The kinetics and the course of the hydrogenation of nitrobenzene over Raney Ni was further complicated by the formation of intermediates, the amounts of which depended on the reaction temperature.[71]

Lieber, Smith, and co-workers found that the addition of chloroplatinic acid to Raney Ni just prior to the start of hydrogenation increased markedly the activity of the catalyst beyond that which could be expected on the basis of platinum metal involved.[72,73] The promoting effect of platinum was also observed in the hydrogenation of various aromatic nitro compounds.[2,73,74] In the hydrogenation of nitrobenzene (0.05 mol) in 120 ml of ethanolic solution at room temperature and atmospheric pressure, the rate was increased from 115 ml (H_2 uptake per 100 sec) over Raney Ni alone to 261 ml when 0.375 mmol chloroplatinic acid (0.073 g Pt) was added to 4.5 g Raney

Ni. The hydrogenation of nitrobenzene was completely inhibited by the addition of 3 mmol (0.012 g) of sodium hydroxide to 4.5 g of Raney Ni, even in the presence of chloroplatinic acid, if the sodium hydroxide was added prior to chloroplatinic acid. The poisoning effect of alkali was also observed in the hydrogenation of isomeric nitrotoluenes and nitrophenetholes. The *ortho* isomers of nitrotoluenes, nitroanilines, nitrophenols, and nitrophenetholes were invariably hydrogenated the fastest, while the *para* isomers were hydrogenated the slowest.[73] The promoting effect of chloroplatinic acid was more pronounced when the rate of hydrogenation was small, as observed in the hydrogenation of the sodium salts and methyl and ethyl esters of isomeric nitrobenzoates. In the most prominent example with ethyl *p*-nitrobenzoate, the rate was increased from 3.9 ml H_2 uptake per 100 s to 502 ml with addition of 0.375 mmol chloroplatinic acid to 4.5 g Raney Ni.[74]

The kinetic studies over platinum metals on the hydrogenation of aromatic nitro compounds have been reported by several investigators. Hernandez and Nord studied the hydrogenation of *meta*- and *para*-substituted nitrobenzenes over colloidal rhodium and palladium catalysts prepared with use of poly(vinyl alcohol) as a protective colloid.[75,76] The hydrogenation over the colloidal rhodium was first-order with respect to the substrate and markedly influenced by both the pH of the ethanol used as solvent and the nature of the substituents. On the other hand, the hydrogenation over the colloidal palladium was first-order with respect to hydrogen pressure and zero-order with respect to the substrate; the rates of hydrogenation were affected neither by the nature of the substituents nor by the acidity of the solution. Smith and Bedoit, Jr. studied the hydrogenation kinetics of various nitrobenzenes over Adams platinum in acetic acid at 30°C and found that the hydrogenations were zero-order with respect to nitrobenzenes and first-order with respect to hydrogen pressure in a range of 0.17–0.50 MPa.[1] The activation energies for mononitrobenzenes were in the range of 13.4 kJ (3.2 kcal)·mol^{-1} for *o*-nitrophenol to 17.1 kJ (4.1 kcal)·mol^{-1} for *o*- and *m*-nitrotoluenes. Within experimental error the substitution of a single methyl group into nitrobenzene did not affect the rate of hydrogenation. Yao and Emmett reexamined the hydrogenation kinetics of *para*-substituted nitrobenzenes over colloidal rhodium and palladium.[77] The results indicated that the catalytic behavior of palladium was essentially the same as that of rhodium. The hydrogenation was first order with respect to hydrogen pressure within a pressure range of 0.020–0.099 MPa. With *p*-nitrophenol as substrate it was shown that with both rhodium and palladium the apparent reaction order with respect to the substrate depended on the amount of catalyst: was first-order at low concentration of catalyst and approached zero-order as the amount of catalyst increased. Under the same experimental conditions the rate of hydrogenation was greater over palladium than over rhodium and reached zero-order at lower amounts of catalyst over palladium than over rhodium. The substituents of nitrobenzene affected the rate of hydrogenation only when the reaction was first-order or fractional-order with respect to the nitro compound. The energy of activation was in the range of 50.2–62.7 kJ (12–15 kcal)·mol^{-1} under the conditions leading to fractional- or first-order with respect to the substrate, while it was only a few kilocalories per mole under zero-order conditions with respect to the substrate where the rate was limited by diffusion

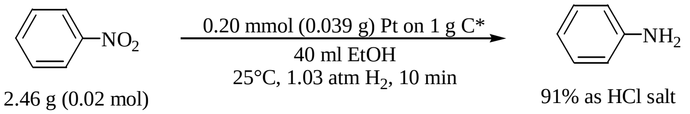
of hydrogen through the solvent to the catalyst surface. The same kinetic behavior was also observed in the hydrogenation of *para*-substituted nitrobenzenes over colloidal platinum.[78] Rajadhyaksha and Karwa studied the hydrogenation of *o*-nitotoluene over a Pd–C in methanol at 90°C.[79] The hydrogenation was zero-order in concentration of the substrate for a conversion of more than 90% and 0.3-order in hydrogen pressure in a range of 0.69–4.14 MPa with an activation energy of 34.36 kJ (8.21 kcal)·mol^{-1}. The rate of hydrogenation, however, was found to increase with increasing initial concentration of nitrotoluene, which appeared incompatible with the zero-order kinetics. The activation energy was also found to be lower by 4.6 kJ·mol^{-1} with an initial concentration of 45% w/w (0.16 mol fraction) of *o*-nitrotoluene in methanol than that with 30% w/w (0.09 mol fraction) initial concentration. The phenomenone was explained by a change in the properties of reaction medium and hence its interaction with the adsorbed species. The effects of solvents in the *o*-nitrotoluene hydrogenation have also been discussed. The results described above appear to indicate that the hydrogenation kinetics of aromatic nitro compounds may depend on the reaction conditions such as the amount and nature of catalyst, solvent, temperature, and hydrogen pressure, as well as the reactivity of nitro compounds.

Karpenko compared the rates of hydrogenation of nitrobenzene over 5% Pd–C, 5% Pt–C, 5% Rh–C, and 5% Ru–C (0.15 g) in methanol at room temperature and atmospheric pressure.[3] The rates, expressed in ml H_2·min^{-1}, were 70 for Pd–C > 40 for Pt–C > 10 for Rh–C > 0 for Ru–C, and nitrobenzene was hydrogenated 8–30 times more rapidly than nitropropane. Taya studied the hydrogenation of various *para*-substituted nitrobenzenes over Pichler's ruthenium dioxide that had been activated at 70°C for 30 min in a hydrogen atmosphere.[80] The rate of hydrogenation in 80 vol% of ethanol at 25°C and atmospheric pressure was in the following order: *p*-nitrobenzonitrile, *p*-nitrobenzoic acid > *p*-nitrophenol > *p*-chloronitrobenzene, nitrobenzene, *p*-nitroanisole, *p*-nitroaniline, *p*-nitrotoluene, *p*-bromonitrobenzene. The rate of hydrogenation of *p*-nitrophenol in water–ethanol and water–dioxane was increased with increasing water content and became the highest in water solution. The hydrogenation of 1 mmol (0.14 g) of *p*-nitrophenol over 7.5 mg of the catalyst was complete within 30 min in an aqueous solution. The addition of 0.5 ml of 10% sodium hydroxide solution to 25 ml 80 vol% of ethanol increased the rates of hydrogenation of *p*-nitrotoluene, *p*-nitroanisole, *p*-nitroaniline, and *p*-nitrophenol. Brown and Sivasankaran compared the activities of six unsupported and carbon-supported platinum metals, prepared by reduction of their salts with sodium borohydride in ethanol, in the hydrogenation of nitrobenzene in ethanol–hydrochloric acid at 25°C and hydrogen pressure 25 mm above atmospheric.[81] The results shown in Table 9.4 indicate that with both the unsupported and the carbon-supported catalysts palladium and platinum are definitely more active for the hydrogenation of nitrobenzene than the other platinum metals. The carbon support increased the rate of the hydrogenation by a factor of 4–5. The in situ–prepared carbon-supported palladium and platinum catalysts were approximately twice as active as commercial 5% Pd–C and Pt–C catalysts. Equation 9.38 shows the hydrogenation of nitrobenzene over the carbon-supported platinum in situ prepared by borohydride reduction.

TABLE 9.4 Hydrogenation of Nitrobenzene over Platinum Metal Catalysts Produced In Situ by Borohydride Reduction[a,b]

	Unsupported Catalyst		Carbon-Supported Catalyst	
Catalyst[c]	Time (min)	Reaction (%)	Time (min)	Reaction (%)
Ru	60	3	60	3
Rh	60	25	60	85
Pd	49	100	12	100
Os	60	6	60	6
Ir	60	20	60	34
Pt	46	100	10	100
5% Pd–C[d]	—	—	24	100
5% Pt–C[d]	—	—	23	100

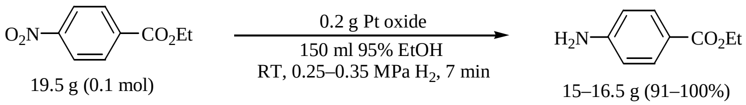
[a]Data of Brown, H. C.; Sivasankaran, K. *J. Am. Chem. Soc.* **1962**, *84*, 2828. Reprinted with permission from American Chemical Society.
[b]For the catalyst preparation and the reaction conditions, see eq. 9.38.
[c]0.2 mmol metal or 0.2 mmol metal on 1 g carbon (Darko K-B) for 20 mmol nitrobenzene.
[d]Commercial catalysts.



(9.38)

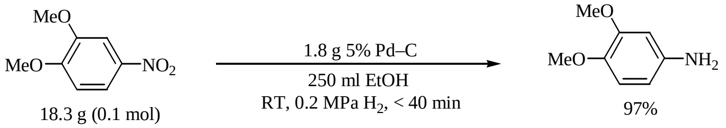
* 1.0 ml of 0.2*M* solution of Pt salt in 40 ml ethanol was reduced with 5.0 ml of 1.00*M* solution of $NaBH_4$ in ethanol in the presence of 1.0 g carbon (Darco K-B), followed by addition of 4.0 ml conc. hydrochloric acid.

Adams et al. studied the effects of medium on the hydrogenation of aromatic nitro compounds over Adams platinum oxide in 95% ethanol at 25–30°C and 0.25–0.35 MPa H_2.[82] The hydrogenation of nitrobenzene in ethanol was retarded by the presence of more than 10% of water. The addition of 0.1 mol of hydrochloric acid to 150 ml of ethanol containing 0.1 mol of nitrobenzene retarded the hydrogenation only slightly. The hydrogenation, however, was retarded significantly by increasing amounts of added hydrochloric acid. Similarly, the hydrogenation was slightly depressed by the addition of 0.1 mol of acetic acid. Larger amounts of acetic acid caused further decrease in the rate. A distinct poisoning effect of sodium hydroxide was observed with addition of as little as 0.025 mol. An example of the use of platinum oxide is shown in eq. 9.39 for the hydrogenation of ethyl *p*-nitrobenzoate.[83] The effect of hydrochloric acid may depend on the nitro compound hydrogenated. For example, the hydrogenation of 4-nitropyrogallol over platinum oxide in 95% ethanol proceeded much faster when 1 equiv of HCl was added before hydrogenation, and the resulting solution of 4-aminopyrogallol hydrochloride was much lighter in color.[84]



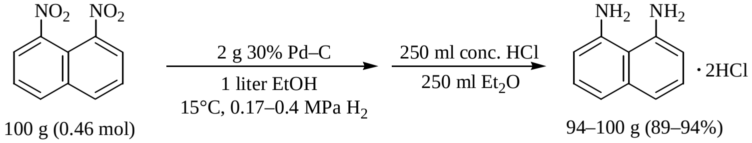
(9.39)

Palladium catalysts, in particular, in the form supported on carbon have frequently been employed for the hydrogenation of aromatic nitro compounds and are often preferred to platinum oxide because of their high activity as well as less tendency toward hydrogenation of the aromatic ring.[85,86] 3,4-Dimethoxynitrobenzene was hydrogenated to 4-aminoveratrole in a 97% yield over 5% Pd–C in ethanol at room temperature and 0.2 MPa H_2 (eq. 9.40).



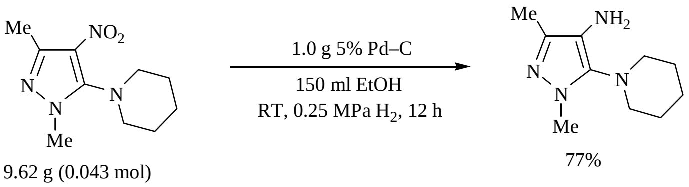
(9.40)

1,8-Dinitronaphthalene was readily hydrogenated over 30% Pd–C in ethanol at low hydrogen pressure to 1,8-diaminonaphthalene, isolated as the crystalline dichloride in excellent yield (eq. 9.41).[85] Use of Adams platinum in the hydrogenation gave a red solution and a blue-gray product. Attempts to use Raney nickel catalysts of various types and under a variety of conditions were always unsuccessful.



(9.41)

In the hydrogenation of some nitropyrazoles, the inhibitory effect of the ring nitrogen was most pronounced with platinum, less with nickel, and least with Pd–C.[87] The hydrogenation of 1,3-dimethyl-4-nitro-5-(1-piperizino)pyrazole was completed in 12 h over 10.4 wt% of 5% Pd–C (0.52% Pd) (eq. 9.42), while, over platinum oxide, about 4 wt% of catalyst was required for the completion of hydrogenation. The hydrogenation of 5-nitroisoquinoline was hydrogenated within several hours over 5% Pd–C in methylcellosolve at room temperature and 0.2–0.3 MPa H_2 (eq. 9.43). The reaction time was decreased by the addition of an equivalent of acetic acid. The hydrogenation with use of 20 wt% of Raney Ni required 18 h even after a second addition of catalyst, and the yield of 5-aminoisoquinoline was only 72%.[88]



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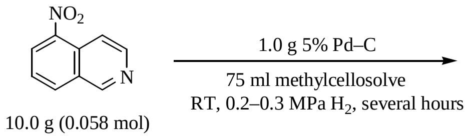
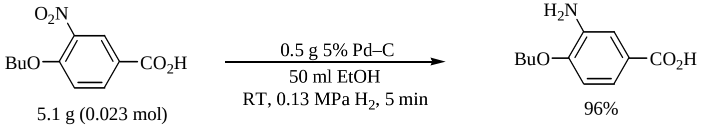


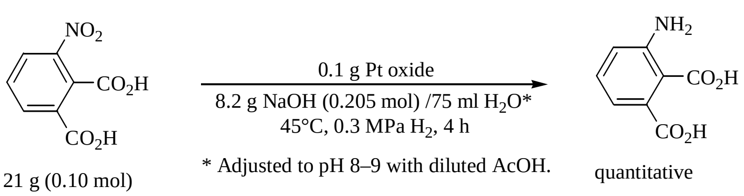
(9. 43)

Nitrobenzoic acids may be hydrogenated to the corresponding amino acids in methanol or ethanol, or in aqueous alkaline solution, over Pd–C, platinum oxide or Raney Ni.[86,89] An example of the hydrogenation over Pd–C is shown in eq. 9.44.[90]



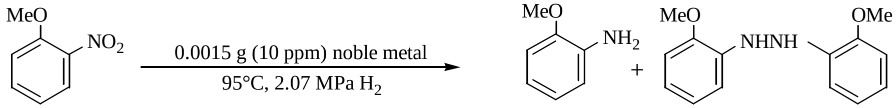
(9.44)

Hydrogenation of 4-nitrosalicylic acid over Pd–C in alcoholic hydrogen chloride was reported to give only a 20% yield of 4-aminosalicylic acid.[91] Hydrogenation of the nitro acid over platinum oxide in ethanol was slow. However, high yields of 4-aminosalicylic acid were obtained in hydrogenation over Raney Ni in a methanol suspension or in water containing an equivalent of sodium hydrogen carbonate.[92] Both 3- and 4-nitrophthalic acids were converted to the corresponding aminophthalic acids in essentially quantitative yields by hydrogenation of their disodium salts in an aqueous solution adjusted to pH 8–9 with acetic acid, over platinum oxide at 45°C and 0.3–0.15 MPa H_2 (eq. 9.45) or over Raney Ni at 70°C and 10 MPa H_2.[93] For the hydrogenation of the 4-isomer with Raney Ni, small amounts of amino or nitro acids, such as 3-amino- and 3-nitrophthalic acids, 4-aminophthalic acid, *m*-aminobenzoic acid, and *p*-amino- and *p*-nitrobenzoic acids, were found to function as accelerators. Without these accelerators, 4-nitrophthalic acid was recovered unchanged.



(9.45)

Kosak studied the hydrogenation of *o*-nitroanisole in details over palladium- and platinum-based catalysts at 95°C and 2.07 MPa H_2.[94] The hydrogenation of *o*-nitroanisole over palladium catalysts was always accompanied by the formation of *o,o′*-hydrazoanisole, the amount of which varied significantly with different samples of starting *o*-nitroanisole. Impurities such as *o*-chloronitrobenzene and *o,o′*-dichloroazoxybenzene present in *o*-nitroanisole were found to increase formation of the hydrazo compound with decrease in the yield of *o*-anisidine, while *o*-chloroanisole had no effect on the composition of the product. The hydrazo compounds were resistant to further hydrogenation under the conditions. Platinum-based catalysts were insensitive to the impurities and always gave *o*-anisidine of high purity. The results are summarized in eq. 9.46.



153 g (1 mol)

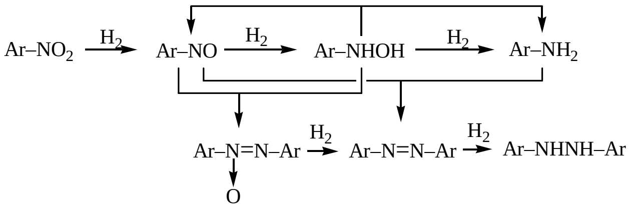
(9.46)

o-Nitroanisole	Catalyst	Product composition (%)	
A	4.5% Pd–0.5% Pt–5.0% Fe–C (USP 2,823,235)	94–97	3–1
A	5% Pt–2.5% Ni-2.5% Cr-C (USP 3,546,297)	99–99.2	< 0.1
B	5% Pd–C (Engelhard Ind.)	80–81.1	16
B	4.5% Pd–0.5% Pt-5.0% Fe-C	91–94	7–4
B	5% Pt–C (Engelhard Ind.)	98–98.4	0.5–0.3
B	5% Pt–2.5% Ni-2.5% Cr-C	98.7–99.0	0.1
C	4.5% Pd–0.5% Pt-5.0% Fe-C	82–85	14–12
C	5% Pt–2.5% Ni-2.5% Cr-C	97–98	2–1

Composition of *o*-nitroanisole (%)	A	B	C
o-Chloroanisole	0.05	0.09	0.09
o-Chloronitrobenzene	0.11	0.25	0.60
o-Nitroanisole	99.82	99.56	98.87
o,o'-Dichloroazoxybenzene	0.01	0.05	0.33
o-Nitrophenol (ppm)	<10	<10	<10

Palladium catalysts were severely poisoned by hydrogen chloride, the presence of which, however, had only a small effect on the product composition. The strong poisoning of palladium with only small amounts of hydrogen chloride may be due to the fact that the hydrogenations were performed in the absence of a hydroxylic solvent, although some water might be formed during hydrogenation.[95] On the basis of the results described above, Kosak suggested that the presence of *o*-chloronitrobenzene, *o,o*′-dichloroazobenzene, and *o,o*′-dichloroazoxybenzene was responsible for the formation of *o,o*′-hydrazoanisole. *o*-Chloronitrobenzene as well as *o*-nitroanisole may lead to the formation of the azo, azoxy, and hydrazo compounds through their hydrogenation intermediates by the reaction paths shown in Scheme 9.9, which involve disproportionation of an arylhydroxylamine to arylnitroso and arylamino compounds.

The catalytic hydrogenation of aromatic nitro compounds is an industrially important process for the preparation of aromatic amines that are used as intermediates for the manufacture of polyurethanes, rubber chemicals, agricultural products, dyestuffs, photographic chemicals, and drugs, as well as various other chemicals. Strätz has com-

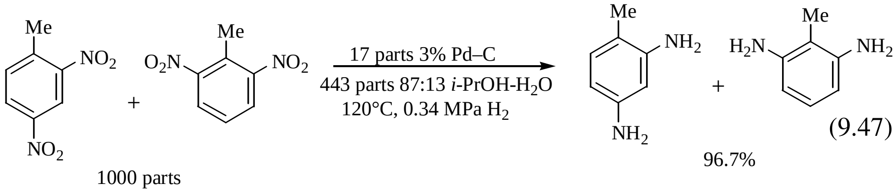


Scheme 9.9 Reaction pathways of aromatic nitro compounds leading to the formation of azoxy, azo, and hydrazo compounds.

prehensively reviewed various processes for the production of aromatic amines, including those from historical to more recent developments.[96] Aniline and toluenediamine are the amines prepared industrially in the greatest amounts, the largest portion of which are used for the manufacture of the isocyanates to make polyurethanes.

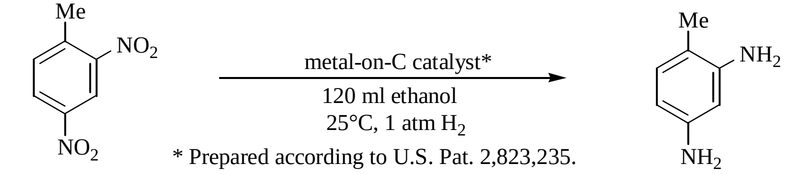
The hydrogenation of nitrobenzenes to anilines is carried out in a liquid phase or in a vapor phase, in either a fixed-bed or a fluidized-bed reactor. For vapor-phase processes, copper-based catalysts[97] and sulfided nickel[98] are among those most frequently used. For liquid-phase processes, supported nickel[99] and Raney Ni[100] as well as supported palladium[101] are the catalysts most commonly employed.

The hydrogenation of dinitrotoluenes to toluenediamines is performed exclusively in the liquid phase at relatively low temperatures to avoid a runaway reaction. Dinitrotoluenes are usually hydrogenated in methanol at temperatures from 50 to 130°C and hydrogen pressures of 0.2–20 MPa. An example of the hydrogenation using Pd–C catalyst is shown in eq. 9.47.[101a]



(9.47)

A carbon-supported palladium containing platinum and iron proved to show excellent activity in the hydrogenation of 2,4-dinirotoluene. The Pd (4.5%)–Pt (0.5%)–Fe (5%) supported on carbon was originaly developed by Dupont using an oleophilic carbon with a surface area of only 50 $m^2 \cdot g^{-1}$. In this study, 0.5% of the Pd was replaced with Pt to enhance its activity and the Fe present as the hydrated oxide effectively depressed its activity for the hydrogenation of the aromatic ring. The rate of hydrogenation of this trimetallic catalyst in the hydrogenation of *o*-nitrotoluene (120°C, 3.4 MPa H_2) was found to be about twice as great as that of 5% Pd–C.[102] The hydrogenation of 2,4-dinitrotoluene in ethanol over this type of catalyst with one modification that activated carbon instead of carbon black was used is shown in eq. 9.48. The reaction time was half that for the catalyst containing palladium only. It is noted that the activity of the palladium catalyst containing platinum only was lower than that of the catalyst containing palladium only.[96]



(9.48)

* Prepared according to U.S. Pat. 2,823,235.

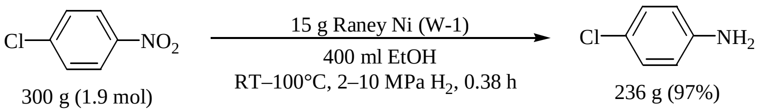
5 g (0.0275 mol, 99.4% purity)

Catalyst (concentration: 2.5%)	Time (min)	Yield (%)(GC)
5% Pd	41	99.3
4% Pd-0.4% Pt	60	99.4
3.5% Pd-0.4% Pt-4.2% Fe	20	99.3

9.3.2 Halonitrobenzenes

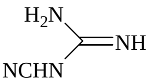
The hydrogenation of halonitrobenzenes to haloanilines is always accompanied by some extent of hydrogenolysis to give dehalogenated anilines. The ease of the hydrogenolysis depends on the nature as well as the ring position of the halogen, increasing generally in the order F < Cl < Br < I and *meta* < *para* < *ortho*.[103–105] The susceptibility to dehalogenation also depends on the nature and amount of catalyst,[106] the support,[104] and the solvent[107,108] as well as on the reaction temperature and hydrogen pressure.[103,105] Palladium catalysts are known to show greater tendency toward dehalogenation than platinum.[104,109,110] The amino group in the aromatic ring labilizes the halogens, regardless of position, and this effect of the amino group may be suppressed by the presence of excess acid.[109] In general, platinum, rhodium, iridium, rhenium, and nickel appear to be preferred catalysts that show less tendency toward dehalogenation and give high yields of haloanilines, although palladium catalysts may be employed successfully for the compounds with less labile halogens.[111]

Winans hydrogenated aromatic halonitro compounds over Raney Ni in ethanol at temperatures below 150°C, and preferably below 125°C.[103] Under these conditions, *o*-, *m*-, and *p*-chloronitrobenzenes and 2,5-dichloronitrobenzene were hydrogenated to the corresponding chloro- and dichloroanilines in more than 90% yields. An example with *p*-chloronitrobenzene is given in eq. 9.49. Even at 150°C, *p*-chloronitrobenzene gave rise to *p*-chloroaniline in nearly quantitative yield. *p*-Bromonitrobenzene was more susceptible to dehalogenation, but still *p*-bromoaniline was obtained in 83% yield. *o*-Iodonitrobenzene was largely dehalogenated, and *o*-iodoaniline was isolated in only 23% yield. 2,4-Dinitrochlorobenzene was extensively hydrogenolyzed to give *m*-phenylenediamine in 91% yield, even when the reaction temperature was maintained below 40°C.

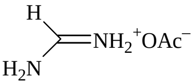


(9.49)

The dechlorination may be depressed markedly in the presence of a suitable inhibitor. For example, 100 g of *p*-chloronitrobenzene was hydrogenated to give 98% *p*-chloroaniline containing 0.3% of *o*-chloroaniline and only 0.08% of aniline over 7 g of Raney Ni in the presence of 1 g of potassium thiocyanate in 300 ml of 95% methanol at 90–100°C and 0.5–1 MPa H_2.[112] Similarly, with potassium thiocyanate and dicyandiamide (**19a**)[113] as inhibitors, *o*-chloronitrobenzene was hydrogenated to *o*-chloroaniline in 99.8 and 99.87% yields, respectively, over Raney Ni in methanol at below 120°C and 1 MPa H_2.

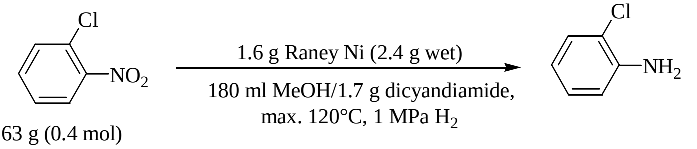


19a



19b

Strätz compared Raney Ni without inhibitor with the Raney Ni poisoned by dicyandiamide in the hydrogenation of *o*-chloronitrobenzene in methanol below 120°C and 1 MPa H_2. Proportion of dechlorination decreased from 44.3% without inhibitor to 0.3% in the presence of the inhibitor, and the yield of *o*-chloroaniline increased from 54.5% without inhibitor to 98.8% with the inhibitor. The dechlorination decreased further to 0.2%, and the yield of *o*-chloroaniline increased to 99.3% over a Raney Ni promoted with chromium and iron (eq. 9.50).[114] Similarly, dehalogenation over the chromium- and iron-promoted Raney Ni was only 0.6% with *m*-chloronitrobenzene, 0.2% with 3,4-dichloronitrobenzene, and 0.5% with *p*-bromonitrobenzene.

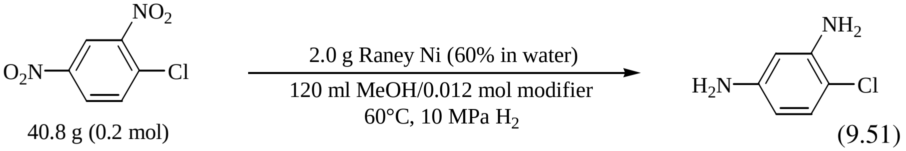


(9.50)

Catalyst	Reaction time (min)	Dechlorination (%)†	Yield (%)†
Raney Ni*	20	44.3	54.5
Raney Ni	27	0.3	98.8
Raney Ni promoted by Cr and Fe	20	0.2	99.3

* Without inhibitor. †Analyzed by GC.

Baumeister et al. studied the hydrogenation of various halonitrobenzenes using Raney Ni modified with amidine derivatives.[115] Formamidine acetate (**19b**) has been found to be the most effective inhibitor for dehalogenation. It has been shown that the dehalogenation occurs as a consecutive reaction after the halogenated aniline has been formed. A typical example with use of this inhibitor is shown in eq. 9.51 for the hydrogenation of 1-chloro-2,4-dinitrobenzene in comparison with dicyandiamide. It is noted that the reaction time could be shortened with **19b** compared to that with **19a**.



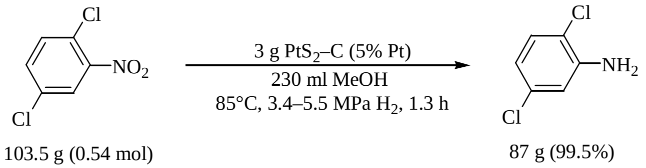
(9.51)

Modifier	Reaction time (min)	Selectivity (%)
Formamdine acetate	75	97.5
Dicyandiamide	210	99
No modifier	240	70

Moreau et al. studied the selectivity of industrial sulfided hydrotreating catalysts such as $NiO–MoO_3–\gamma\text{-}Al_2O_3$ and $CoO–MoO_3–\gamma\text{-}Al_2O_3$ in the hydrogenation of chloronitrobenzenes to chloroanilines at temperatures ranging from 50 to 250°C and 2 MPa H_2.[116] The reaction proceeded through rapid hydrogenation of the nitro group (k_1 in $\times 10^3\cdot min^{-1}\cdot g\ cat^{-1}$) followed by slow cleavage of the C–Cl bond (k_2 in $\times 10^3\cdot min^{-1}\cdot g\ cat^{-1}$) of the intermediate chloroanilines. The maximum concentration of *p*-chloroaninline was calculated to increase from 72% at 250°C (k_1/k_2 = 349/49) to 85% at 200°C

(k_1/k_2 = 250/12) and 95% at 150°C (k_1/k_2 = 85/1) over sulfided 2.7% NiO–16.5% MoO_3–80.8% Al_2O_3. The results were better over sulfided 3% CoO–14% MoO_3–83% Al_2O_3, 77% at 250°C (k_1/k_2 = 235/25), 94% at 200°C (k_1/k_2 = 215/3) and 98% at 150°C (k_1/k_2 = 149/0.5).

Platinum catalysts have been shown to be highly selective for the hydrogenation of halonitrobenzenes to haloanilines. A number of effective platinum catalysts or catalyst systems have been described in the literature, mostly in patents.[96] Dovell and Greenfield found that the sulfides of the platinum metals and cobalt were highly selective in the hydrogenation of halo-substituted nitrobenzenes.[117–119] There was no detectable dechlorination with the sulfides of palladium, platinum, rhodium, ruthenium, and cobalt; no detectable debromination occurred with platinum sulfide; trace debromination occurred with rhodium sulfide and cobalt sulfide; and appreciable debromination occurred with palladium sulfide. Typical hydrogenations with 5% platinum sulfide on carbon catalyst are given in eqs. 9.52 and 9.53 with 2,5-dichloronitrobenzene and *p*-bromobenzene, respectively.[118]



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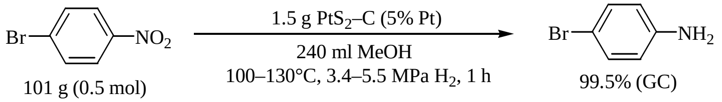


(9.53)

Some of other effective platinum catalysts are sulfided platinum on carbon[120] or platinum catalysts with inhibitors such as bis(2-hydroxyethyl)sulfide,[121] morpholine,[122] polyamines,[123] phosphorous acid,[105] phosphoric acid,[124] and dicyandiamide.[96] Dicyandiamide was originally used as an effective inhibitor for Raney Ni, as described above (see eq. 9.50).[113] Hydrogenations of halonitrobenzenes with use of these platinum catalysts are summarized in Table 9.5. In one patent, it is claimed that ethanolamine is a better inhibitor than morpholine for Pt–C. Thus, 3,4-dichloronitrobenzene was hydrogenated over Pt–C modified with iron oxide in the presence of 1.2 mol% ethanolamine to give 3,4-dichloroaniline containing only 235 ppm of 4-chloroaniline, compared to 548 ppm with morpholine as the inhibitor.[125]

Pascoe studied the selective hydrogenation of isomeric bromonitrobenzenes to bromoanilines with commercially available 5% Pt–C–S, 5% Pt–C, 5% Rh–C, and Raney Ni in ethanol or tetrahydrofuran as solvent at room temperature and 0.41 or 10.3 MPa H_2 but without any inhibitor.[108] In general, 5% Rh–C gave good yields in the hydrogenation of the three isomers with minimum debromination, and 5% Pt–C was effective for the hydrogenation of the *ortho* and *para* isomers. Debromination was lesser in tetrahydrofuran than in ethanol for the *ortho* and *para* isomers, while ethanol was the preferred solvent for the *meta* isomer. For the *para* isomer in tetrahydrofuran, 5%

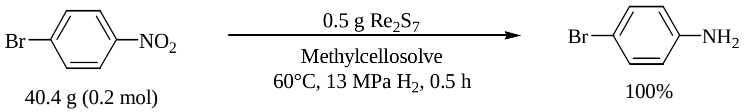
TABLE 9.5 Hydrogenation of Halonitrobenzenes to Haloanilines over Platinum Catalysts

Nitrobenzene	Catalyst/Inhibitor	Solvent	*T* (°C)	H_2 *P* (MPa)	Haloaniline (%)[a]	Ref.
2-Chloro-	Sulfided 5% Pt–C[b]	MeOH	≤125	1	> 99.8	96
2-Chloro-	1% Pt–C/$(HOCH_2CH_2)_2S$	PhMe	100	1	99.97	121
2-Chloro-	5% Pt–C/H_3PO_3	—	110–115	3.4	98.3	105
2-Chloro-	5% Pt–C/morpholine	—	95–100	3.4	99.2	—[c]
2-Chloro-	5% Pt–C/tetraethylenepentamine	—	100	<5	99.5	123
2-Chloro-	1% Pt–C/H_3PO_4	—	—	—	99.0	124
2-Chloro-	5% Pt–C/dicyandiamide	MeOH	≤125	1	>99.8	96
3-Chloro-	Sulfided 5% Pt–C[b]	MeOH	≤125	1	>99.8	96
4-Chloro-	Sulfided 5% Pt–C[b]	MeOH	≤125	1	>99.8	96
4-Chloro-	5% Pt–C/H_3PO_3	—	100–115	3.4	99.6	105
3-Chloro-4-methyl	Sulfided 5% Pt–C[b]	MeOH	≤ 125	1	> 99.8	96
3,4-Dichloro	5% Pt–C/morpholine	—	95–100	3.4	99.5	105
3,4-Dichloro-	5% Pt–C/$(PhO)_3P$	—	95–100	3.4	98.5	105
3,4-Dichloro-	5% Pt–C/triethylenetetramine	—	100	<5	98.5	123
2,5-Dichloro-	5% Pt–C/H_3PO_3	—	95–100	3.4	98.4	105
4-Bromo-	Sulfided 5% Pt–C[b]	MeOH	≤ 125	1	99.8	96
3-Iodo-	5% Pt–C/H_3PO_3	MeOH	50–55	3.4	93	105

[a]GC analysis.
[b]Degussa F 103 RSH catalyst sulfided according to Ref. 120b.
[c]Kosak, J. R. *Ann. NY Acad. Sci*. **1970**, *172*, 175.

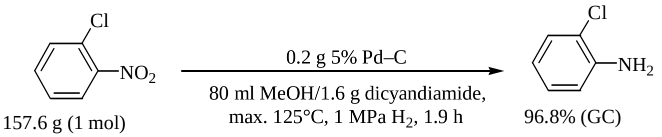
Pt–C–S was the best catalyst. The best results as expressed by the molar ratio of bromoaniline to aniline were as follows: 143 for the *ortho* isomer (5% Pt–C in THF at 10.3 MPa H_2), 150 for the *meta* isomer (5% Pt–C in EtOH at 10.3 MPa H_2), and 77 for the *para* isomer (5% Pt–C–S in THF at 10.3 MPa H_2). The rate of hydrogenation and the amount of azoxy intermediate formation, which depended on the isomer reduced, were greatest with the *para* isomer and smallest with the *ortho* isomer. This was explained by the stereochemistry that the large *ortho*-bromo group would hinder the reaction between the nitroso and hydroxylamine intermediates. Since at no time during hydrogenation were any intermediates, either partly or completely dehalogenated, detected, it was deduced that dehalogenation occurred after the bromoaniline had been formed. Some rearrangement of the *para* isomer to the *ortho* and *meta* isomers occurred during hydrogenation. Since there was no detection of either *ortho*- or *meta*-isomer contamination in the starting *para* isomer and trace amounts of rearranged hydroxylamine intermediate were detected during hydrogenation, it was suggested that the rearrangement occurred either at the nitroso intermediate or during its hydrogenation to the hydroxylamine.

Iridium and rhenium catalysts, although applied in relatively few cases, have been reported to be highly selective for the hydrogenation of halonitrobenzenes to haloanilines. The hydrogenation of 3,4-dichloronitrobenzene with 5% Ir–C in isopropyl alcohol afforded the corresponding dichloroaniline almost quantitatively (98.8% at the maximum, compared to 97.0% with 5% Pt–C).[126,127] The rate of the dechlorination over the iridium catalyst was only $\frac{1}{250}$th the rate of the hydrogenation. Broadbent et al. found that the aromatic nitro group was easily hydrogenated at room temperature or slightly higher over rhenium heptasulfide, without accompanying dehalogenation with halonitrobenzenes.[128] Thus, *p*-bromonitrobenzene was hydrogenated quantitatively to *p*-bromoaniline over rhenium heptasulfide in methylcellosolve at 60°C and 13.1 MPa H_2 (eq. 9.54). The same selective hydrogenation was also achieved over rhenium(III) oxide in ethanol at 124°C and 22.2 MPa H_2.[129]



(9.54)

Palladium catalysts, although usually more sensitive to hydrodehalogenation than platinum, may be employed successfully in the hydrogenation of halonitrobenzenes with less labile halogens. For example, *p*-chloroaniline and 2,5-dichloroaniline were manufactured by hydrogenation of the corresponding halonitrobenzenes over 3% Pd–C in isopropyl alcohol or water at 100°C in the presence of triethyl phosphite.[130] Hydrogenation of *o*-chloronitrobenzene over Pd–C in the presence of triethyl phosphite and dicyandiamide (eq. 9.55) gave *o*-chloroaniline in 96.7 and 96.8% yields, respectively.[131] Dechlorination decreased from 52% without inhibitor to 2.8% in the presence of dicyandiamide, which was even smaller than the amount of dechlorination over sulfided Pd–C (5.4%).



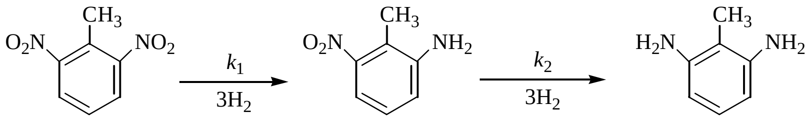
(9.55)

Smith et al. studied the effect of particle size on the hydrogenation and hydrodechlorination of *p*-chloronitrobenzene over 5% Pd–C and several Pd–SiO_2 catalysts with varying degrees of dispersion. The smaller palladium crystallites catalyzed the hydrogenation at about the same rate, but the hydrodechlorination at rates passing through a minimum around the catalyst with 60% exposed palladium. Addition of cadmium acetate depressed hydrodechlorination to a larger extent than hydrogenation, resulting in a better selectivity for *p*-chloroaniline.[132]

A rather high activity of Pd–C catalyst toward dechlorination was utilized for the preparation of fluoroanilines from chlorofluoronitrobenzenes. Thus, 3,5-difluoroaniline was obtained by hydrogenation of 2,6-dichloro-3,5-difluoronitrobenzene over Pd–C in the presence of tertiary, water-insoluble amines, such as tris(C_8–C_{10} alkyl)amines as an acid trap.[133]

9.3.3 Hydrogenation of Dinitrobenzenes to Aminonitrobenzenes

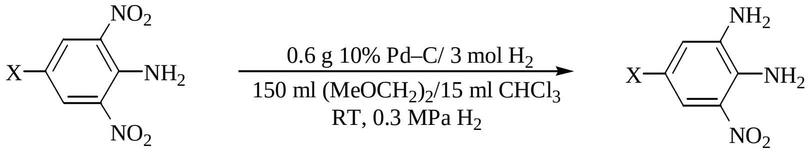
By using suitable reaction conditions and catalysts, dinitrobenzenes may be hydrogenated to aminonitrobenzenes in rather high yields, especially with the dinitro compounds where regioselectivity is not a concern. Kut et al. studied kinetically the consecutive hydrogenation of 2,6-dinitrotoluene (DNT) to 2-amino-6-nitrotoluene (ANT) and 2,6-diaminotoluene (DAT) (Scheme 9.10) over supported platinum metal catalysts in ethanol at the temperatures of 40–75°C and hydrogen pressures of 0.5–10 MPa.[134] Under similar conditions, platinum and rhodium catalysts were more selective for intermediate ANT formation than were palladium catalysts. The selectivity of Pt–Al_2O_3 catalysts increased with decreasing metal content, although the activity decreased somewhat. Thus, the maximum yields of ANT increased from 46% with 5% Pt–Al_2O_3 to 83% with 0.1% Pt–Al_2O_3. The selectivity decreased with increasing reaction temperature and was independent of the hydrogen pressure above 3 MPa, where the reaction was zero-order in hydrogen pressure. Under the conditions where mass transfer effects did not concern and with use of a 0.5% Pt–Al_2O_3 (particle diameter <45 μm), the k_1/k_2 and b_{DNT}/b_{ANT} ratios were 6.50 and 50.0, respectively, at 40°C, where the k_i and b_i values are, respectively, pressure-independent rate constants and adsorption coefficients for DNT and ANT. The selectivity factor k_1b_{DNT}/k_2b_{ANT} was



Scheme 9.10 Consecutive hydrogenation of 2,6-dinitrotoluene to 2-amino-6-nitrotoluene and 2,6-diaminotoluene.

325 at 40°C, and a maximum yield of ANT as high as 98.2% was obtained. At 60°C, however, k_1/k_2 and b_{DNT}/b_{ANT} were 14.38 and 4.20, respectively, and the selectivity factor and the maximum yield of ANT decreased to 60.4 and 93.3%, respectively.

Lyle and LaMattina selectively hydrogenated 4-substituted 2,6-dinitroanilines to the corresponding nitrophenylenediamines over 10% Pd–C in 1,2-dimethoxyethane–chloroform as solvent (eq. 9.56).[135] With use of ethanol instead of 1,2-dimethoxyethane, 4-trifluoromethyl-2,6-dinitroaniline was completely hydrogenated to give the corresponding triaminobenzene.

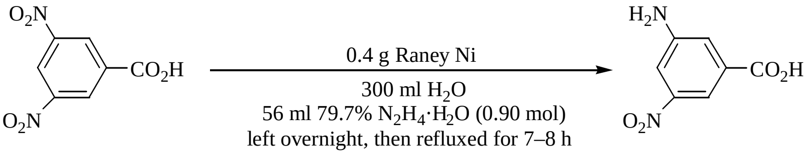


0.6 mol

	Reaction time (h)	Yield (%)
X = CO_2Et	15	63
CO_2H	3	89
CF_3	1	58
Me	1.5	81

(9.56)

Aromatic dinitro compounds may be selectively reduced by hydrazine in the presence of transition metal catalysts.[136] Pitrè and Lorenzotti obtained 3-amino-5-nitrobenzoic acid in 82% yield by treating 3,5-dinitrobenzoic acid with Raney Ni and an appropriate amount (3.6 equiv) of hydrazine in water (eq. 9.57).[137] Similarly, 2,4-dinitrophenol and 2,4-dinitroaniline were reduced to 2-amino-4-nitrophenol and 2-amino-4-nitroaniline, respectively, with 10% Pd–C and hydrazine in ethanol solution.



53 g (0.25 mol) 37.2 g (82%) (9.57)

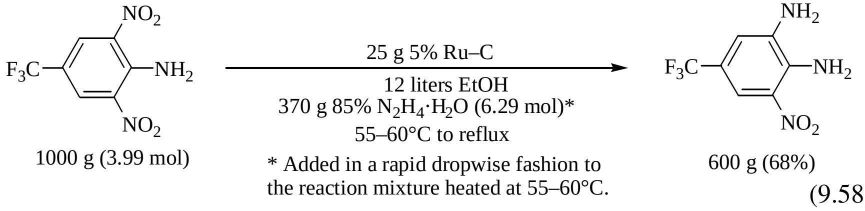
Miesel et al. reduced various 4-substituted 2,6-diniroanilines and 5- or 6-substituted 2,4-dinitroanilines to the corresponding 2-amino-6-nitro- and 2-amino-4-nitroanilines, respectively, by hydrazine in the amount from theoretical to 5–10% excess in the presence of 5% Ru–C in ethanol.[138] Several catalysts were compared for the selectivity in the reduction of 4-trifluoromethyl-2,6-dinitroaniline (Table 9.6). The results indicate that 5% Ru–C is the most selective catalyst, but 5% Pd–C may also be employed. However, the selectivity greatly decreases with 5% Ru–Al_2O_3. A large-scale run of the reduction of 4-trifluoromethyl-2,6-dinitroaniline is shown in eq. 9.58. The reduction of 2,4-dinitroanilines was not so facile as the reduction of 2,6-dinitoanilines. 2,4-Dinitroanilines with 5-amino, 5-trifluoromethyl, 6-trifluoromethyl, and 6-chloro (eq. 9.59) groups were cleanly reduced under similar conditions. Reduc-

TABLE 9.6 The Reduction of 4-Trifluoromethyl-2,6-dinitroaniline with Hydrazine in the Presence of Catalyst in Ethanol[a]

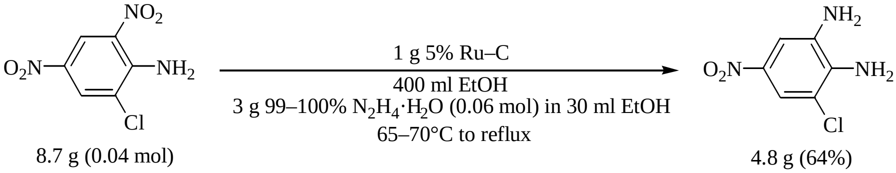
	Relative Proportions of Products			
Catalyst	Aniline	Diamine	Triamine	Other
5% Ru–C	4	96	—	—
5% Pd–C	6	88	6	—
5% Pt–C	8	82	3	7
5% Rh–C	—	47	6	47
5% Ru–Al_2O_3	—	60	10	30
Raney Ni	Mixture too complex to analyze			

[a]Data of Miesel, J. L.; O'Doherty, G. O. P.; Owen, J. M. in *Catalysis in Organic Syntheses 1976*; Rylander, P. N.; Greenfield, H., Eds.; Academic Press: New York, 1976; p 283. Reprinted with permission from Academic Press Inc.

tion of 5-chloro-2,4-dinitroaniline, however, was unsuccessful because of the phenylhydrazine formation arising from displacement of the active halogen. In all cases, reduction of 6-alkyl-2,4-dinitroanilines gave a mixture of diamine, triamine, and unreacted aniline. As the alkyl group became more bulky, the proportion of triamine increased.



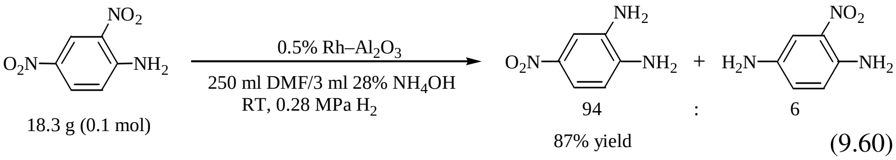
(9.58)



(9.59)

Alaimo and Storrin found that 2,4-dinitroaniline was selectively hydrogenated to 2-amino-4-nitroaniline by hydrogenation in *N,N*-dimethylformamide over 5% Rh–Al_2O_3 in the presence of ammonium hydroxide (eq. 9.60).[139] The product ratio of 2-amino-4-nitro- to 4-amino-2-nitroaniline was 94:6 in DMF, compared to 15:85 in ethanol. The hydrogenation in DMF also proceeded in a moderate rate to the reduction of one nitro group and then essentially stopped. Some degree of selectivity (92:8) was also obtained with platinum oxide in DMF when the hydrogenation was interrupted after one nitro group had been reduced in order to prevent further hydrogenation. Over

5% Pd–C in both ethanol and DMF, little, if any, selectivity was obtained; product ratios were 50:50 in ethanol and 60:40 in DMF. Palladium black in ethanol, which afforded 4-amino-5-nitroveratrole in 70–75% yield from 4,5-dinitroveratrole, provided no selectivity with 2,4-dinitroaniline, as well as with *o*- and *m*-dinitrobenzenes; both nitro groups were hydrogenated.[140] Reduction by sodium borohydride and Pd–C in methanol also does not appear to be selective, as 1,2,4-triaminobenzene is formed.[141] It is of interest that over Pt–C in acidic alcohol 2,4-dinitroaniline is selectively hydrogenated at the 4-nitro group to give 4-amino-2-nitroaniline in 70% yield.[142]

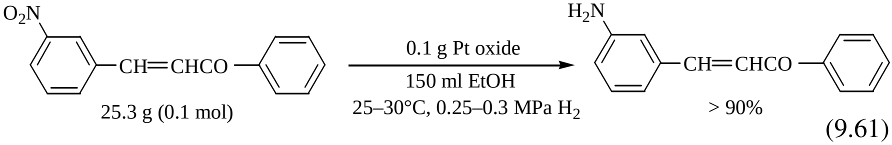


(9.60)

When 2-nitro group is sterically hindered by a substituent at the 1 position, the 4-nitro group may be selectively hydrogenated to give the 4-amino-2-nitro compound. Raney Cu was found to be highly selective for this type of selective hydrogenation.[143] For example, 2,4-dinitro-1-propylbenzene was selectively hydrogenated to the corresponding 4-amino-2-nitro compound over Raney Cu in xylene at 150°C and 1.4 MPa H_2. Under the same conditions hydrogenation of 2,4-dinitroanisole gave only 2,4-diaminoanisole while 1-(*N*-piperidyl)-substituted 2,4-dinitrobenzene was hydrogenated to the corresponding 4-amino-2-nitro compound in more than 99% yield.

9.3.4 Selective Hydrogenations in the Presence of Other Unsaturated Functions

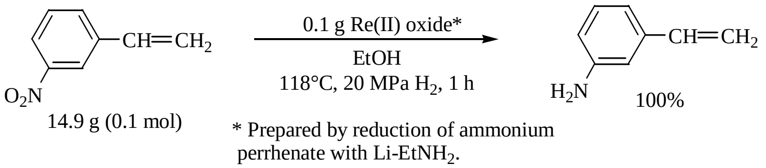
The aromatic nitro group may be preferentially hydrogenated in the presence of α,β-unsaturated functions. For example, *m*-nitrobenzalacetophenone (eq. 9.61) and *m*-nitrobenzalacetone were quantitatively hydrogenated to the corresponding *m*-amino compounds over platinum oxide in ethanol with absorption of only 3 equiv of hydrogen. Similar results were also obtained with ethyl *m*-nitrocinnamate, although a little more than 3 equiv of hydrogen was absorbed in this case. On the other hand, with the addition of 0.15 mol of acetic acid for 0.1 mol of substrate, the absorption of hydrogen proceeded until both the nitro and olefinic groups were completely hydrogenated.[82]



(9.61)

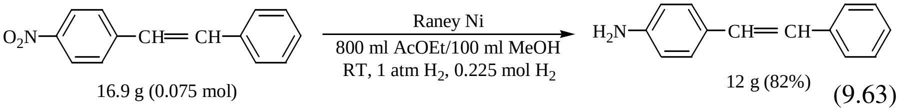
Blout and Silverman selectively hydrogenated nitrocinnamic acids and esters (5 g) to the corresponding amino compounds over Raney Ni (2–3 g, wet) in ethanolic suspension (50 ml) at 20–30°C and 0.2–0.3 MPa H_2.[144] The rate of hydrogen absorption dropped to between 0.3 and 0.01 of its former value after the uptake of 3 equiv of hy-

drogen. In all cases the acids were hydrogenated more slowly than the corresponding methyl esters. In order to obtain the *o*-amino compounds, it was necessary to stop the hydrogenation immediately after the absorption of the calculated amount of hydrogen. On further hydrogenation, hydrocarbostyril (**20**) was obtained in high yields (Scheme 9.11). The yields of amino compounds were 73–84% for the *meta* and *para* acids and their methyl esters, and 37% for the *ortho* acid and 74% for the *ortho* methyl ester. 3-Nitrostyrene was selectively hydrogenated to 3-aminostyrene over rhenium(II) oxide (eq. 9.62)[145] or polysulfides of group VIII metals (e.g., CoS_3).[146]

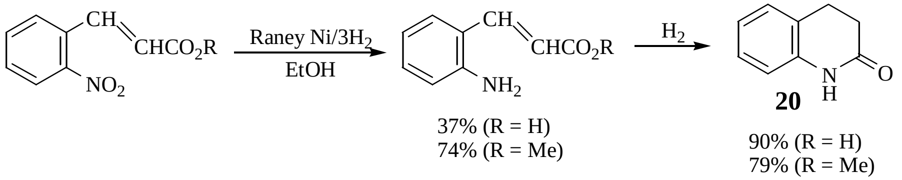


(9.62)

The hydrogenation of nitrostilbenes to aminostilbenes was reported with not always consistent results.[147–150] Bergmann and Schapiro observed that during hydrogenation of nitrostilbenes with Pd–$BaSO_4$ or Raney Ni, no marked change in the rate took place after absorption of 3 mol of hydrogen.[148] If the hydrogenation was interrupted at this point, only the completely reduced aminodiphenylethane was isolated. According to Drefahl and Ulbricht, however, in the hydrogenation of 4-nitrostilbene over Raney Ni in ethyl acetate–methanol, a distinct change in the rate was observed after uptake of 3 mol of hydrogen and 4-aminostilbene was obtained in 82% yield by interrupting the hydrogenation at this point (eq. 9.63).[150] In contrast, hydrogenation of 2- and 3-nitrostilbenes proceeded with no such change in rate during hydrogenation, in accord with the results by Bergmann and Schapiro. Benoit and Marinopoulos, however, could obtain 3-aminostilbene in Raney Ni–catalyzed hydrogenation of 3-nitrostilbene.[149] Ruggli and Dinger obtained *cis*- and *trans*-2,4′-diaminostilbenes in 93 and 82% yields, respectively, by hydrogenation of the corresponding dinitrostilbenes over Raney Ni in ethyl acetate until the hydrogen uptake ceased.[147]



(9.63)



Scheme 9.11 Hydrogenation of *o*-nitrocinnamic acid and ester over Raney Ni.

Onopchenko et al. studied preferential hydrogenation of aromatic nitro groups in the presence of acetylenic bonds.[151,152] The selectivities of noble metal and Raney nickel catalysts have been compared in the hydrogenation of 3-nitrophenylacetylene in isopropyl alcohol at room temperature and 0.34 MPa H_2. The results summarized in Table 9.7 show that ruthenium is highly selective for the formation of 3-aminoacetylene, although the catalyst life appears to be limited. Ru–C was active at room temperature, while Ru–Al_2O_3 and ruthenium dioxide required temperatures of 50°C or higher. Rh–Al_2O_3 and Raney Ni were nonselective at room temperature, but their selectivities were improved in hydrogenation at –30°C. In contrast, palladium and platinum catalysts provided largely the products selectively hydrogenated at the ethynyl group, *m*-nitrostyrene and *m*-nitroethylbenzene.

Among the sulfides of molybdenum, cobalt, nickel, iron, rhodium, rhenium, osmium, and ruthenium, only the polysulfide of cobalt[153] and the sulfide of ruthenium showed good selectivities. Optimum conditions over cobalt polysulfide included temperatures of 85–120°C, hydrogen pressures of 2.8–6.9 MPa, substrate concentrations of up to 25%, and substrate:catalyst ratios of 50–80:1 (g of feed/g of Co). A typical run is shown in eq. 9.64. The hydrogenation over ruthenium disulfide was successful

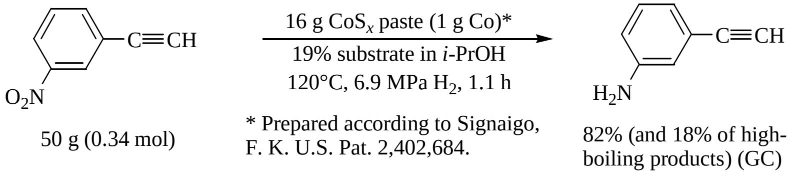
TABLE 9.7 Selectivity of Transition Metal Catalysts in Hydrogenation of 3-Nitrophenylacetylene (NPA)[a,b]

			% Selectivity (GC)[c]				
Catalyst	T (°C)	NPA Conversion (%)	APA	AS	NS	NEB	EA
5% Os–C	100	73	22	18	42	13	5
5% Ru–C	25	92	96	3	—	1	—
5% Ru–Al_2O_3	60	90	90	5	3	1	1
RuO_2 (0.15 g)	50	43	96	3	—	1	—
5% Pd–$BaSO_4$	26	100	—	—	58	38	4
5% Pd–C	26	100	—	—	2	81	15
5% Pd–asbestos	25	85	—	—	66	34	—
5% Pd–$CaCO_3$	25	100	—	—	30	60	10
Raney Ni	24	96	38	18	26	7	11
Raney Ni	–30	10	47	3	41	—	9
5% Rh–Al_2O_3	24	78	13	10	53	—	24
5% Rh–Al_2O_3	–30	37	53	1	33	13	—
PtO_2 (0.15 g)	25	81	1	6	67	24	2

[a]Data of Onopchenko, A.; Sabourin, E. T.; Selwitz, C. M. in *Catalysis of Organic Reactions*; Kosak, J. R., Ed.; Marcel Dekker: New York, 1984; p 269. Reprinted with permission from Marcel Dekker Inc.

[b]3-Nitrophenylacetylene (NPA)(2 g) was hydrogenated over 1 g catalyst in 130 ml *i*-PrOH at 0.34 MPa H_2 (6.9 MPa H_2 for Os–C).

[c]*key*: APA, 3-aminophenylacetylene; AS, 3-aminostyrene; NS, 3-nitrostyrene; NEB, 3-nitroethylbenzene; EA, 3-ethylaniline.



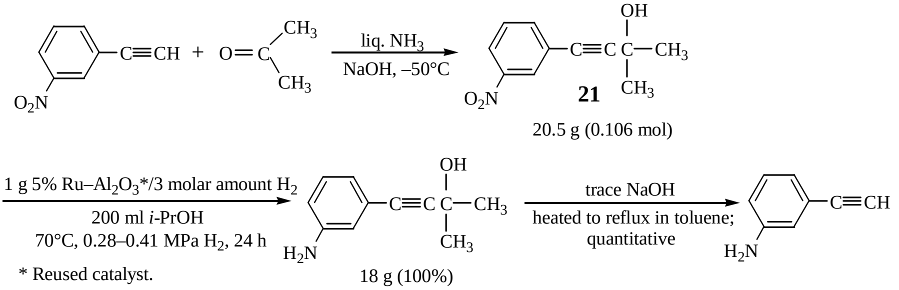
(9.64)

only at low substrate concentrations (<5%) because of the formation of condensation products at higher concentrations.[152]

Although 3-nitrophenylacetylene was selectively converted to the aminoacetylene over ruthenium, the catalyst was found to be poisoned during hydrogenation. Onopchenko et al. suggested that the deactivation would result from a too-strong adsorption of the terminal ethynyl group (probably of the amino product), rather than from the formation of the condensation products. Therefore, the ethynyl group was blocked by the reaction with acetone in liquid ammonia and the resulting 2-methyl-4-(3-nitrophenyl)-3-butyn-2-ol (**21**) was hydrogenated to the corresponding amino compound in essentially quantitative yields. It was necessary to stop the reaction at the stoichiometric point because hydrogenation of the triple bond took place, although at a slower rate. Successful reuse of the catalyst was demonstrated, with no loss in activity and selectivity. Removal of the protecting group was effected by heating in the presence of a catalytic amount of sodium hydroxide to give a quantitative yield of 3-aminophenylacetylene of >98% purity (Scheme 9.12).[151]

9.3.5 Hydrogenation Accompanied by Condensation or Cyclization

The products of the hydrogenation of nitrobenzenes may be subject to condensation with other unsaturated groups such as carbonyl or carbonyl-containing groups and cyano or cyano-containing groups. The condensation may occur especially readily when such a group is located at a position that may give a five- or six-membered cyclic product. These reductive cyclizations have been widely utilized in the synthesis of compounds containing nitrogen hetreocyclic rings. The condensation may occur either at the amino group or at an intermediate stage before the nitro group is reduced to amino, in particular at the hydroxylamino stage.

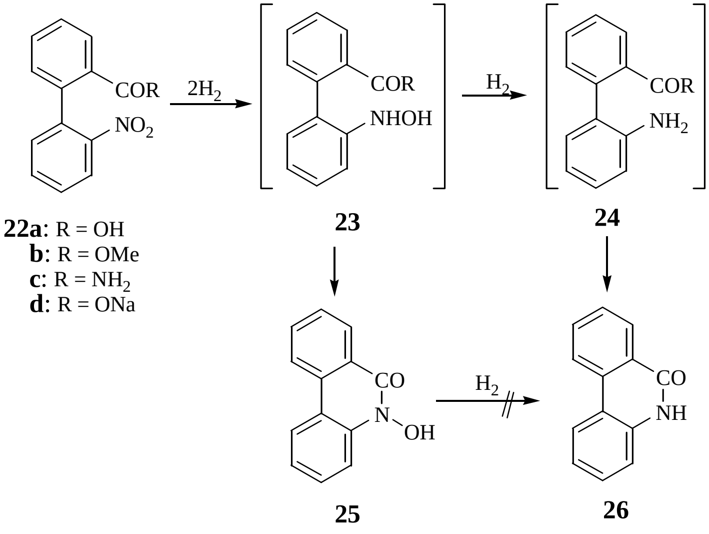


Scheme 9.12 Synthesis of 3-aminophenylacetylene from 3-nitrophenylacetylene via hydrogenation of the dimethylcarbinol derivative.

Muth et al. studied the hydrogenation and cyclization of 2-nitro-2′-carboxybiphenyl and its carboxy derivatives (**22a**–**22d**) over platinum oxide in ethanol (Scheme 9.13).[154] *N*-Hydroxyphenanthridone (**25**) was considered to result from the cyclization at the hydroxylamino compound **23**, and phenanthridone (**26**) to result from the amino compound **24** and not via **25**, since **25** did not undergo the reduction to yield phenanthridone under the conditions of the reaction.

As seen from the results shown in Table 9.8, which were based on the moles of hydrogen absorbed per mole of the nitro compound, in all cases a higher percentage of condensation at the hydroxylamine **23** occurred in the presence of mineral acid. In the absence of mineral acid the condensation at **23** decreased with respect to the carboxyl function in the order $CO_2H > CO_2CH_3 > CONH_2$ with no cyclization in the last case. In contrast, this order was reversed in the presence of mineral acid. The higher percentages of cyclization in the presence of mineral acid were explained by assuming that the carbonyl function to react with the hydroxylamino group would be protonated and thus would become a better electrophile. Since the carbamoyl group is the strongest base of the groups compared, its conjugate acid is the weakest and should be the best electrophile, which may thus explain the highest percentage in the formation of **25** with **22c**. No cyclization at **23** occurred with the sodium salt **22d**; only phenanthridone (**26**) and sodium 2-amino-2′-biphenylcarboxylate (**24d**) were formed.

Similar cyclization at the hydroxylamine may also take place in the presence of a cyano group.[154–156] In the hydrogenation of 2-nitro-2′-cyanobiphenyl (**27**) over platinum oxide in ethanol, 6-aminophenanthridine *N*-oxide (**28**) was the sole compound produced. Compound **28**, which was suggested to be in equilibrium with **29**, was obtained in 90% yield in the hydrogenation in tetrahydrofuran in which **27** was more soluble than in ethanol (eq. 9.65).[154]

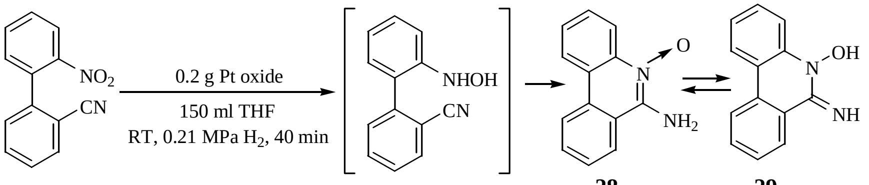


Scheme 9.13 Hydrogenation and cyclization of 2′-substituted 2-nitrobiphenyls.

TABLE 9.8 Hydrogenative Cyclization of 2′-Substituted 2-Nitrobiphenyls[a,b]

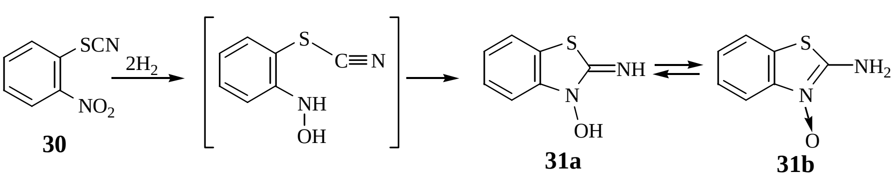
2′-Substituent	H_2 Uptake (mol/mol)	Cyclization at Hydroxylamine (%)
CO_2H	2.49	51
CO_2H (H^+)[c]	2.33	67
CO_2Me	2.60	40
CO_2Me (H^+)[c]	2.25	75
$CONH_2$	—	0[d]
$CONH_2$ (H^+)[c]	2.14	86
CO_2Na	—	0[e]

[a]Data of Muth, C. W.; Elkins, J. R.; DeMatte, M. L.; Chiang, S. T. J. *Org. Chem.* **1967**, *32*, 1106. Reprinted with permission from American Chemical Society.
[b]A total of seven aliquots in each 50-ml aliquot of substrate (1.0 mmol) in ethanol were hydrogenated over 0.037 g of prereduced platinum oxide in 20 ml ethanol at room temperature and 0.1–0.2 MPa H_2.
[c]Hydrogenated in the presence of 1 drop (0.05 ml) of concentrated sulfuric acid.
[d]Only phenanthridone was isolated.
[e]Phenathridone was isolated, and sodium 2-amino-2′-biphenylcarboxylate was detected.



27 9.33 g (0.046 mol) **28** 8.75 g as monohydrate (90%) **29** (9.65)

Cyclization at the hydroxylamine also occurs in the hydrogenation of 1-nitro-2-thiocyanatobenzene (**30**) to give 2-aminobenzothiazole 3-oxide (**31**) (Scheme 9.14).[157] The hydrogenation over Raney Ni in ethanol at room temperature and 0.3 MPa H_2 was complete after several hours with absorption of 2 mol of hydrogen to give crude **31** in 75–88% yield. The infrared spectrum of the product **31** indicated the presence of an equilibrium between **31a** and **31b**. Under similar conditions but with use of platinum oxide in tetrahydrofuran, **31** and its 5-methyl, 5-methoxy, and 5-chloro derivatives were prepared in 81–91% yields.[158]

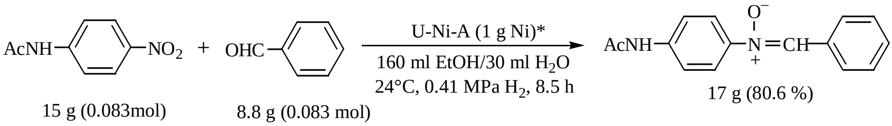


30 **31a** **31b**

Scheme 9.14 Hydrogenative cyclization of 1-nitro-2-thiocyanatobenzene.

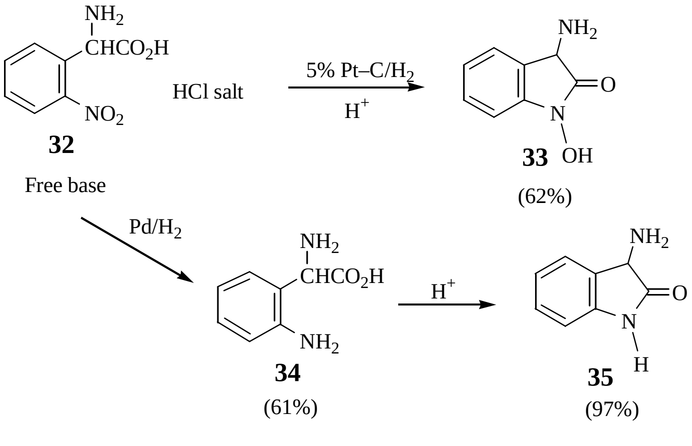
Hydrogenation of *o*-nitrophenylglycine (**32**) as hydrochloride over 5% Pt–C under acidic conditions afforded 3-amino-1-hydroxy-2-indolinone (**33**), the cyclization product at the hydroxylamino compound, in good yield. On the other hand, hydrogenation of the free base of **32** over a palladium black under neutral conditions gave *o*-aminophenylglycine (**34**), which could be converted to 3-amino-2-indolinone (**35**) by spontaneous cyclization in acidic solution (Scheme 9.15).[159]

Hydrogenation of aromatic nitro compounds in the presence of an aldehyde may give *N*-arylnitrones by condensation of the hydroxylamines formed with the aldehyde. *N*-Arylnitrones have been shown to be valuable substances for introducing either a chlorine or oxygen function into the *ortho* position of a benzene ring containing a nitrogen function.[160] Mylroie et al. have shown that better yields of aryl nitrones can be obtained conveniently by catalytic hydrogenation than by a chemical reduction using zinc and acetic acid. In particular, Urushibara catalysts have been found to be effective in preparing *N*-arylnitrones of excellent quality in high yields.[161] An example is shown in eq. 9.66. In one patent, nitrobenzene was hydrogenated, for instance, in the presence of 4-$Et_2NC_6H_4CHO$ over 5% Pt–C in EtOH–DMSO at 0.28–0.34 MPa H_2 to give 69% of the corresponding nitrones.[162]



*Urushibara Ni prepared using aqueous AcOH. (9.66)

Hydrogenative cyclization of aromatic nitro compounds at the amino group has been described in a number of examples and widely utilized in the synthesis of five- and six-membered *N*-heterocyclic compounds. Walker synthesized 5,6-dimethoxyoxindole and 5,6-dimethoxyindole by hydrogenative cyclization of ethyl 4,5-dimethoxy-

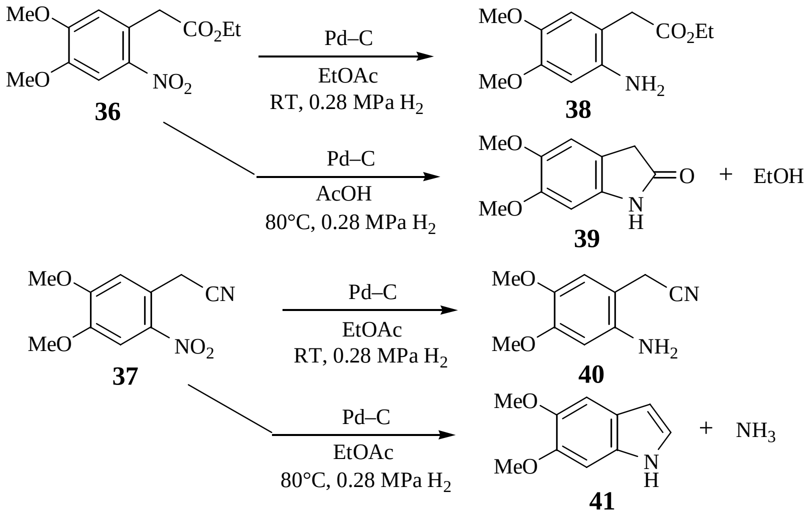


Scheme 9.15 Hydrogenation and cyclization of *o*-nitrophenylglycine.

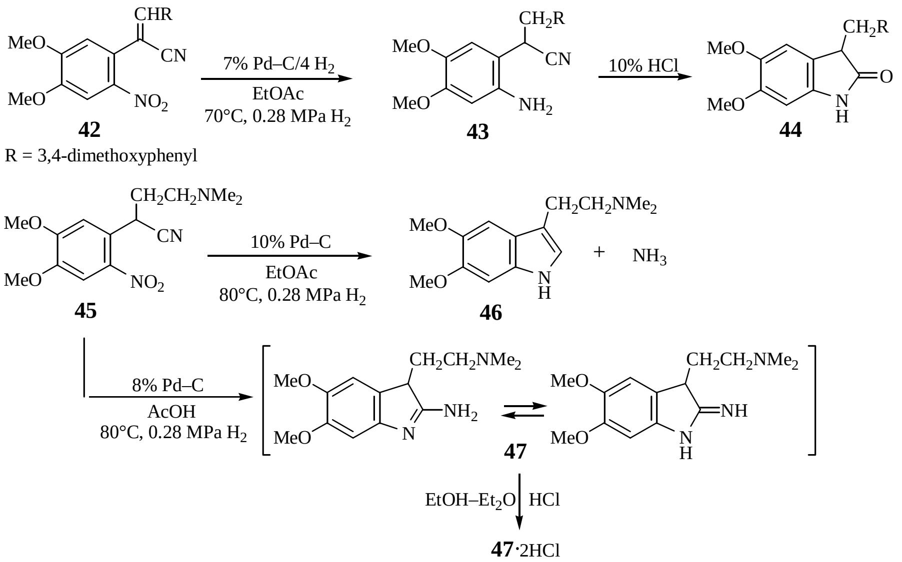
2-nitrophenylacetate (**36**) and 4,5-dimethoxy-2-nitrophenylacetonitrile (**37**), respectively.[163] The hydrogenation of nitroester **36** in ethyl acetate at room temperature and 0.28 MPa H_2 over 7% Pd–C gave the corresponding aminoester **38**, but hydrogenation in acetic acid at 80°C led to the formation of the oxindole (2-indolinone) **39**. For the preparation of **39** the nitroacid may also be used, although a longer time is required for the complete lactam formation than with the nitroester. Like the nitroester **36**, the nitronitrile **37** was hydrogenated to give the aminonitrile **40** in ethyl acetate at room temperature. When the reaction was conducted at 80°C, however, ammonia and 5,6-dimethoxyindole (**41**) were formed with uptake of 4 equiv of hydrogen (Scheme 9.16).

Evidence that aminonitriles and 2-aminoindoles are the intermediates in this cyclization leading to indoles was obtained with α-substituted 2-nitrophenylacetonitriles. The final absorption of 1 mol of hydrogen was slow in the hydrogenation of **42**, ammonia was not formed, and the aminonitrile **43** was the product, which cyclized to the oxindole **44** in the presence of acid. The hydrogenation of β-dimethylaminoethyl-substituted nitronitrile **45** over 10% Pd–C in ethyl acetate at 80°C afforded ammonia and the indole **46**. However, the hydrogenation of **45** over 8% Pd–C in acetic acid at 80°C did not result in the formation of an appreciable amount of ammonia, and a crystalline dihydrochloride corresponding to an amidine structure **47** could be prepared from the product (Scheme 9.17).

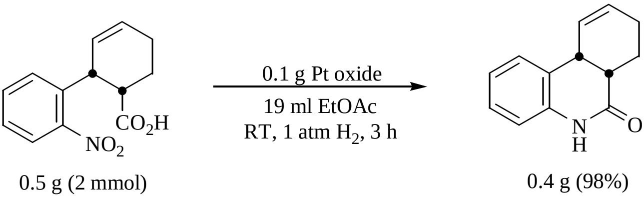
Augustine et al. prepared 2-methylindole in high yield by hydrogenating *o*-nitrophenylacetone, obtained from *o*-fluoronitrobenzene and ethyl acetoacetate, over 5% Pd–C in acetic acid at room temperature and 0.28 MPa H_2 (Scheme 9.18).[164] Examples of utilization of condensation at the amino group for the formation of six-membered nitrogen rings are shown in eqs. 9.67[165] and 9.68.[166]



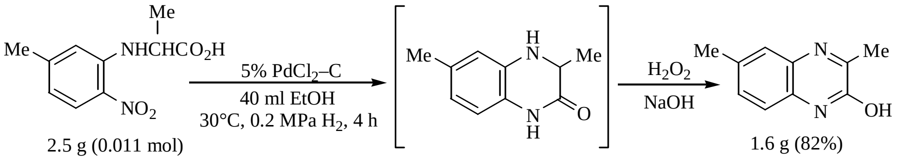
Scheme 9.16 Hydrogenation and cyclization of ethyl *o*-nitrophenylacetate **36** and *o*-nitrophenylacetonitrile **37**.



Scheme 9.17 Intermediates of the hydrogenative cyclization of nitro nitriles leading to indoles.



(9.67)



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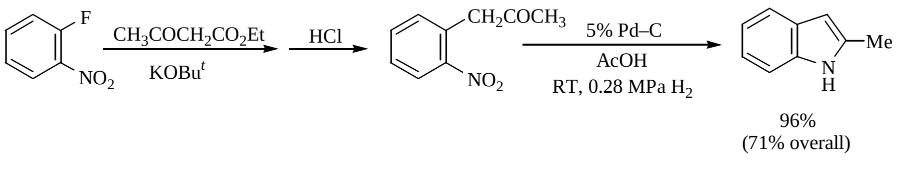


Scheme 9.18 Hydrogenative cyclization of *o*-nitrophenylacetone.

9.3.6 Hydrogenation to Hydroxylamines

Aromatic nitro compounds may be hydrogenated to arylamines either through uncoupled intermediates—nitroso and hydroxylamino compounds—or through coupled intermediates—azoxy, azo, and hydrazo compounds. With use of a suitable catalyst and proper reaction conditions, the hydroxylamines or hydrazo compounds may be obtained in good yields, particularly in the presence of an inhibitor, although only anilines and starting nitrobenzenes have often been found in the reaction mixture at intermediate stages.[2,74]

Accumulation of arylhydroxylamine intermediates during the hydrogenation of aromatic nitro compounds may result in a runaway reaction in indutrial process, as experienced during the hydrogenation of 3,4-dichloronitrobenzene.[167,168] A sudden pressure increase leading to the destructive runaway reaction was attributed to rapid exothermic disproportionation (35 $kcal{\cdot}mol^{-1}$) of the thermally unstable hydroxylamine intermediate to the nitroso and amino compounds, together with an increase in the rate of highly exothermic hydrogenation (62 $kcal{\cdot}mol^{-1}$) of the hydroxylamine intermediate to the amine.

Debus and Jungers[71] and Sugimori[169] isolated *N*-phenylhydroxylamines in Raney Ni–catalyzed hydrogenation of nitrobenzenes. When nitrobenzene was hydrogenated in ethanol over well-washed Raney Ni at 25°C and 1 atm H_2 and the hydrogenation interrupted at an uptake of 2 mol of hydrogen, *N*-phenylhydroxylamine was obtained in a 77% yield, as determined by conversion to azoxybenzene on exposure to air. In the same way, partial hydrogenation of *p*-nitroanisole and ethyl *p*-nitrobenzoate gave the corresponding hydroxylamines in 22 and 60% yields, respectively.[169] In the case of *p*-nitroanisole, *p*-anisidine was also obtained in 40% yield. The rate of hydrogen uptake in the course of hydrogenation monotonously decreased with *p*-anisole, while with nitrobenzene and ethyl *p*-nitrobenzoate the rate increased toward the end of the reaction. This stage in a greater rate was considered to correspond to the hydrogenation of the hydroxylamines to amines. From these observations, Sugimori has suggested that the difference in strength of adsorption between a nitrobenzene and the corresponding hydroxylamine is greater in cases of nitrobenzene and ethyl *p*-nitrobenzoate (with an electron-withdrawing group) than in *p*-nitroanisole (with an electron-releasing group). By this assumption it could be explained why high yields of hydroxylamines were obtained with nitrobenzene and ethyl *p*-nitrobenzoate, even though the corresponding hydroxylamines were hydrogenated faster than the parent nitro compounds. The effect of ring substituents on hydroxylamine accumulation in the hydrogenation of nitroarenes has been discussed by Freifelder,[170] Karwa and Rajadhyaksha,[171] and Rains et al.[168]

In some cases *N*-phenylhydroxylamines were obtained in good yields in palladium-catalyzed hydrogenations.[172–178] Brand and Steiner obtained *N*-phenylhydroxylamine in 80% yield in the hydrogenation of nitrobenzene over 2% Pd–C in a 3:1 mixture of 95% ethanol and water and by interrupting the reaction when 2 mol of hydrogen had been absorbed.[174] In the hydrogenation of *p*-nitrobenzamide and *p*-nitrobenzoic acid over Pd–C in the presence of pyridine and quinoline, respectively, the corresponding hydroxylamino compounds were obtained in 94 and 98% yields, respectively.[179]

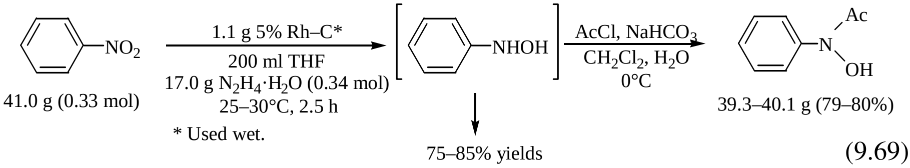
In general, however, platinum, iridium, and rhodium catalysts appear to be more selective than palladium for the formation of hydroxylamines. Rylander et al. obtained high yields of *N*-phenylhydroxylamines in the hydrogenation of nitrobenzenes over Pt–C or Pt–Al_2O_3 in neutral media, especially 80% ethanol, containing small amounts of dimethyl sulfoxide (Me_2SO) without a serious decrease in rate.[180,181] The catalyst system of Pd–C and Me_2SO was much less effective for these partial hydrogenations, in line with the observation that, in competitive hydrogenation of nitrobenzene and phenylhydroxylamine, nitrobenzene was hydrogenated preferentially over platinum, whereas phenylhydroxylamine was hydrogenated preferentially over palladium. According to the procedure by Rylander et al., Karwa and Rajadhyaksha investigated a wide range of operating conditions that might affect the selectivity to phenylhydroxylamine formation, using 5% Pt–C as catalyst.[171] In the hydrogenation at 60°C and 1.46 MPa H_2 in methanol, the maximum selectivity (yield) to phenylhydroxylamine increased from 26% without Me_2SO to 70% with 1.6% (w/w) of Me_2SO concentration. The selectivity to phenylhydroxylamine further increased to 78% at a lower temperature (40°C), but was independent of hydrogen pressure. The variation of product composition with reaction time indicated that aniline and phenylhydroxylamine were formed simultaneously from nitrobenzene. Addition of Me_2SO suppressed the rate of both of the reactions, but more significantly the rate of the aniline formation, thus resulting in improved selectivity to phenylhydroxylamine formation. It appears that adsorption of nitrobenzene is much stronger than that of phenylhydroxylamine, since hydrogenation of phenylhydroxylamine practically does not take place until almost all nitrobenzene has been converted. Polar hydroxylic solvents appear to be favorable for high selectivity to hydroxylamine. Thus, hydrogenation without solvent or in benzene and ethyl acetate gave only low yields (<22%) of phenylhydroxylamine, compared to 67% in isobutyl alcohol, 70% in methanol, and 76% in 18 w/w aqueous methanol.

Chloronitrobenzenes are hydrogenated to give the corresponding chlorohydroxylamines in high yields over Pt–C in the presence of amines, heterocyclic *N*-containing compounds, or other modifiers that are usually added to minimize accompanying dechlorination (see Section 9.3.2). Kosak studied the amounts of hydroxylamine intermediates accumulated in the hydrogenation of various chloronitrobenzenes over 5% Pt–C (Ni–Cr modified) in the presence of morpholine (1 wt%) at 95–100°C and 1.4 MPa H_2.[167] The maximum amounts observed decreased in the order: 3.4-dichloronitrobenzene (35%) > *o*-chloronitrobenzene (~5%) > 2-chloro-4-nitrotoluene (~5.0%) > *p*-chloronitrobenzene (1.9%). In the presence of phosphorous acid a marked increase in maximum hydroxylamine accumulation was observed when 1 wt% of sodium nitrate was added to 3,4-dichloronitrobenzene (~40% at 80% conversion), compared to only about 8% after ~10% conversion in the absence of sodium nitrate.[167] In one patent, 2,5-dichloronitrobenzene (4.75 g) was hydrogenated in 24.4 g of pyridine over Pt–C to yield 3.86 g (87.6%) of 2,5-dichlorphenylhydroxylamine.[182] According to a more recent patent, high yields of aryl-, pyridinyl-, and quinolinylhydroxylamines may be obtained in the hydrogenation of nitro compounds over Pt–C in the presence of *N*-substituted morpholines.[183] For example, hydrogenation of *o*-nitrotoluene over 5% Pt–C in *N*-methylmorpholine at 28–30°C gave a crude product con-

taining 96.4% of *o*-tolylhydroxylamine; the remainder was mostly unreacted starting material. Crystallization of the product gave the pure hydroxylamine in 92% yield. In contrast, when *N*-methylpiperidine was used as solvent, the crude product containing only 86.7% of the hydroxylamine was obtained.[183]

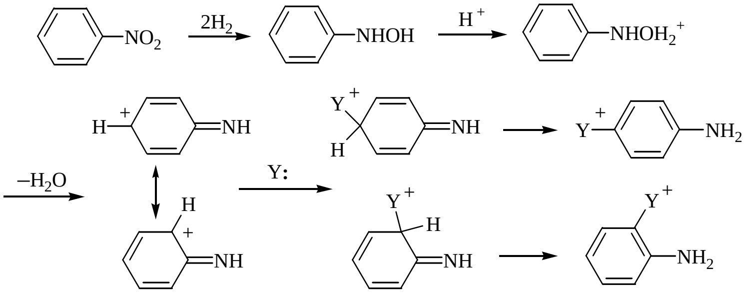
Iridium catalysts have been found to selectively produce hydroxylamines in the hydrogenation of aromatic nitro compounds.[184] Taya found that the hydrogenation of nitrobenzene in ethanol over an Adams-type iridium catalyst at 25°C, and atmospheric pressure became slow markedly after 2 mol of hydrogen had been consumed.[185] By interrupting the hydrogenation at this stage, *N*-phenylhydroxylamine was isolated in a 58% yield. On the other hand, when platinum or palladium catalysts of the Adams type were used, no such decrease in the rate was observed and mainly aniline, and no *N*-phenylhydroxylamine, was obtained with the uptake of 2 mol of hydrogen. A number of substituted nitrobenzenes and 1-nitronaphthalene were also hydrogenated with the iridium catalyst in 20% water–80% ethanol, and the corresponding hydroxylamines were obtained in the following yields: 20% with *o*-methyl-, 77% with *m*-methyl-, 75% with *p*-methyl-, 25% with *o*-chloro-, 73% with *m*-chloro-, 83% with *p*-chloro-, 65% with *p*-bromo-, and 36% with *p*-methoxynitrobenzenes, 69% with 1-nitronaphthalene, and 90% with 2,4-dinitrotoluene (yield of 4-hydroxyamino-2-nitrotoluene).[185] Savchenko et al. observed similar selectivity of iridium for the formation of phenylhydroxylamines in the hydrogenation of nitrobenzenes with use of an Ir–C catalyst prepared by borohydride reduction of iridium salt in isopropyl alcohol.[126] Accumulation of *N*-arylhydroxylamines was favored by a neutral pH, low temperatures, and electron-withdrawing substituents. Maximum yields of arylhydroxylamines were 78% with *p*-bromonitrobenzene, 89% with *p*-chloronitrobenzne, and nearly 100% with *p*-nitrobenzaldehyde, compared to 52% with nitrobenzene and 0% with *p*-nitrophenol, *p*-anisole, and *p*-phenethole.[186]

Catalytic transfer hydrogenation of nitrobenzene over 5% Rh–C in the presence of hydrazine is also effective in giving *N*-phenylhydroxylamine, which was isolated as the *N*-acetyl derivative in 79–80% yield; although not very stable, *N*-phenylhydroxylamine could also be isolated in 75–85% yields (eq. 9.69).[187]



(9.69)

When nitrobenzenes are hydrogenated in an acidic solution, *N*-phenylhydroxylamines formed may undergo an intermolecular nucleophilic rearrangement to give *o*- and *p*-substituted anilines by the reaction sequence shown in Scheme 9.19. Hydrogenation of nitrobenzene in aqueous acid affords *p*-aminophenol (Y: = H_2O in Scheme 9.19). Since *p*-aminophenol is used commercially as a photographic developer as well as for many other applications, there have been a number of patents for the manufacture of it.[188] In the process employing catalytic hydrogenation, nitrobenzene is usually hydro-



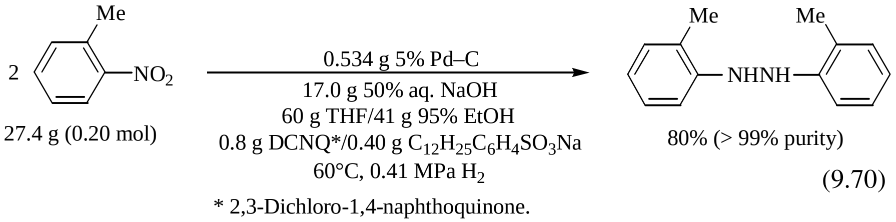
Scheme 9.19 Formation of *ortho*- and *para*-substituted anilines in the hydrogenation of nitrobenzene in an acidic medium.

genated over platinum catalysts in dilute sulfuric acid. Byproducts are aniline and *o*-aminophenol. In one patent, 12.3 g of nitrobenzene was hydrogenated over 0.015 g of 3% Pt–C in 120 g of 15% sulfuric acid containing 0.5 g of formic acid at 80°C and 0.41 MPa H_2 to give 83.3% of *p*-aminophenol and 16.3% of aniline.[189] Hydrogenation in the presence of certain additives such as a quaternary ammonium salt, $Me_3(C_{12}H_{25})N^+Cl^-$,[190] or dimethyl sulfoxide,[180,191] or hydrogenation over sulfided platinum[192] have been reported to give high yields of *p*-aminophenol. Hydrogenation of nitrobenzene in the presence of nucleophiles other than water may lead to formation of *para*-substituted anilines. For example, *p*-fluoroaniline was obtained in 61% yield by hydrogenation of nitrobenzene over platinum oxide in anhydrous hydrogen fluoride at 50°C and 0.38 MPa H_2 (Y: = F^- in Scheme 9.19).[193] Similarly, chloroanilines were obtained by hydrogenation of nitrobenzenes in hydrochloric acid.[194]

9.3.7 Hydrogenation to Hydrazobenzenes

Hydrogenation of nitrobenzenes may give coupled products, azoxy-, azo- and hydrozobenzenes, in particular, in an alkaline medium (see Scheme 9.9). Debus and Jungers isolated hydrazobenzene from the reaction mixture in the hydrogenation of nitrobenzene over Raney Ni at temperatures below 100°C.[71] According to one patent, hydrogenation of *o*-nitrotoluene over an active noble metal catalyst such as palladium black in an alkaline alcohol gave a mixture consisting of 60% *o*-hydrazotoluene and 40% *o*-toluidine.[195] Hydrogenation under similar conditions in the presence of small amounts of 2,3-dichloro-1,4-naphthoquinone and sodium dodecylbenzenesulfonate afforded good yields of *o*-chlorohydrazobenzene from *o*-chloronitrobenzene.[196] In another patent, over 80% yields of *o*-alkylhydrazobenzenes were obtained by a two-step hydrogenation over Pd–C in methanol containing about 20% sodium hydroxide. In the first stage, the temperature was maintained at 20–30°C under 0.55 MPa H_2. When about 1.5 mol of hydrogen had reacted, the temperature was raised over a 2-h period to 90°C and held there until hydrogen absorption ceased. Thus, an 82% yield of *o*-hydrazotoluene, together with 9.2% of *o*-toluidine, was obtained in the hydrogenation of *o*-nitrotoluene.[197] Coe and Brockington studied in details the effects of various factors for the formation of *o*-hydrazotoluene in the hydrogenation of *o*-nitrotoluene using

5% Pd–C.[198] A high yield of *o*-hydrazotoluene was obtained by hydrogenation over 5% Pd–C in a two-phase solution containing alcohol/THF and aqueous sodium hydroxide in the presence of 2,3-dichloro-1,4-naphthoquinone (eq. 9.70).



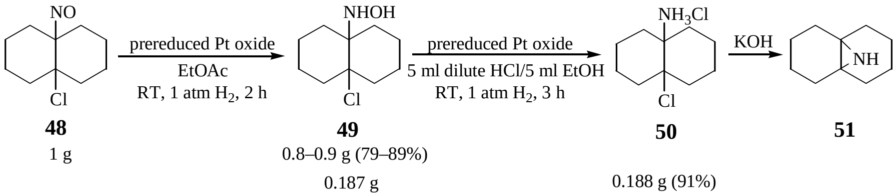
(9.70)

9.4 NITROSO COMPOUNDS

Primary and secondary aliphatic nitroso compounds, with an α-hydrogen, are unstable and readily rearrange to or exist as the more stable tautomeric oximes. Therefore, these nitroso compounds can be understood to be hydrogenated in the form of the oximes. On the other hand, tertiary and aromatic nitroso compounds as well as *N*-nitrosamines may be hydrogenated as the compounds with a true nitroso group.

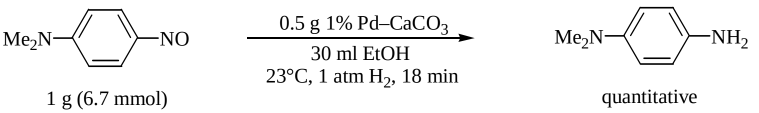
An example of the hydrogenation of a tertiary nitroso compound is given in Scheme 9.20.[199] 9-Nitroso-10-chlorodecalin (**48**), prepared by the addition of nitrosyl chloride to $\Delta^{9,10}$-octalin, was hydrogenated to the hydroxyamino compound **49** over prereduced platinum oxide in ethyl acetate. Compound **49** was further hydrogenated to the amine hydrochloride **50** in ethanolic dilute hydrochloric acid with freshly prereduced platinum oxide. This hydrogenation was utilized to determine the configuration of the adduct **48** to be *trans* by transforming the amine hydrochloride into the aziridine **51** with the action of aqueous potassium hydroxide. Conversion of the nitroso group to the amino group in one step in acetic acid and hydrochloric acid was unsuccessful.

Aromatic nitroso compounds are, like aromatic nitro compounds, hydrogenated rapidly to the amines over palladium catalysts,[200,201] as seen in an example shown in eq. 9.71. However, in contrast to the cases with aromatic nitro compounds, a kinetic



Scheme 9.20 Hydrogenation and reaction of 9-nitroso-10-chlorodecalin.

study of the hydrogenation of *N*-(1,4-dimethylpentyl)-4-nitrosoaniline over 5% Pd–C in toluene at 80°C and hydrogen pressures of 0.57–2.07 MPa indicated that hydrogenation to the corresponding amine could be modeled by first-order kinetics with respect to the concentration of the nitroso compound, and the rate constants became smaller with increasing hydrogen pressure. These results suggested that the nitroso compound was rather weakly adsorbed onto Pd–C and its adsorption was effectively competed by hydrogen at higher pressures.[202] Smith et al. have discussed the hydrogenation of nitrosobenzene and the mechanism and conditions that depress byproduct formation and lead to quantitative formation of aniline.[203]



(9.71)

N-Nitrosamines. Hydrogenation of *N*-nitrosamines over palladium, platinum, and nickel catalysts usually proceeds to give amines, and in rather few cases have *unsym*-hydrazines been obtained in good yields. Amines may also be formed directly from nitrosamines by a rather complex parallel reaction.

Paal and Yao found that the hydrogenation of *N*-nitrosodiphenylamine (R = Ph in Scheme 9.21) over Pd–$CaCO_3$ or Pd–$BaSO_4$ in alcoholic solution at room temperature afforded diphenylamine quantitatively with apparent absorption of only 1 mol of hydrogen.[200] Neither *unsym*-diphenylhydrazine nor ammonia could be detected in the reaction mixture. Further, it was found that 0.5 mol of nitrogen for 1 mol of *N*-nitrosodiphenylamine was evolved. From these findings Paal and Yao concluded that diphenylamine was formed from the *N*-nitrosoamine, according not to reaction **I** but to reaction **II** in Scheme 9.21, which could explain the apparent absorption of 1 mol of hydrogen per mole of the nitrosoamine. It was suggested that the formation of diphenylamine (reaction **II**) occurred through the formation of an intermediate tetraphenyltetrazene according to reaction **III**. Tetraphenyltetrazene was assumed further to be hydrogenated to unstable tetrazane, which was decomposed into 2 mol of diphenylamine and 1 mol of nitrogen (reaction **IV**). The formation of tetraphenyltetrazene by condensation of the starting nitrosamine and the hydrazine, formed by hydrogenation (reaction **V**), appeared unlikely since a mixture of both the components reacted only very slowly and afforded a product that contained no tetraphenyltetrazene. Reaction **II** took place more rapidly in the presence of alkali. On the other hand, in acetic acid solution the nitrosoamine was hydrogenated only slowly and incompletely, and the reaction mixture contained diphenylamine and some diphenylhydrazine besides the starting nitrosamine. In the case of *N*-nitroso-*N*-ethylphenylamine, the quantitative reaction to *N*-ethylaniline (reaction **II**) occurred only in alkaline alcoholic solution. In alcoholic solution *unsym*-ethylphenylhydrazine and ammonia were also found in the reaction mixture together with predominant *N*-ethylaniline. A reaction similar to that in alcoholic solution was also observed in acetic acid, but ammonia was not formed in appreciable amounts. Hydrogenation of *N*-nitrosopiperidine in alcoholic solution proceeded much more slowly, and about 52% of

$$R_2N{-}NO \xrightarrow{2H_2} R_2N{-}NH_2 + H_2O \xrightarrow{H_2} R_2NH + NH_3 \qquad \textbf{(I)}$$

$$R_2N{-}NO + 1.5\,H_2 \longrightarrow R_2NH + 0.5\,N_2 + H_2O \qquad \textbf{(II)}$$

$$2\,R_2N{-}NO + 2\,H_2 \longrightarrow R_2NN{=}NNR_2 + 2\,H_2O \qquad \textbf{(III)}$$

$$R_2NN{=}NNR_2 + H_2 \longrightarrow [R_2NNHNHNR_2] \longrightarrow 2\,R_2NH + N_2 \qquad \textbf{(IV)}$$

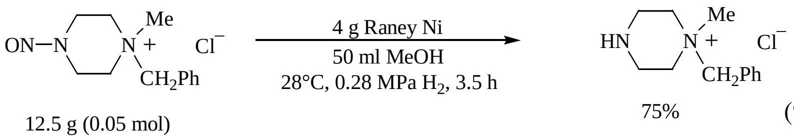
$$R_2N{-}NO + R_2N{-}NH_2 \longrightarrow R_2NN{=}NNR_2 + H_2O \qquad \textbf{(V)}$$

Scheme 9.21 Reactions of *N*-nitrosamine in the presence of palladium catalyst and hydrogen.

N-nitrosopiperidine was converted to piperidine and nitrogen and 4.67% was hydrogenated to the hydrazine, but no ammonia was detected. In acetic acid, piperidine, piepridylhydrazine, and ammonia were formed under absorption of a greater amount of hydrogen. *N*-Nitrosodipropylamine was hydrogenated even more slowly, and 18.5% of the *N*-nitrosoamine was converted to dipropylamine and nitrogen and 3.7% to *unsym*-dipropylhydrazine. Thus, in aryl-substituted nitrosamines, reaction of **II** is much more rapid and more favored over reaction **I** than in dialkylnitrosamines.[200]

Grillot hydrogenated *N*-nitrosodiphenylamine in alcoholic solution, using Raney Ni and Adams platinum oxide as catalysts.[204] The hydrogenation over Raney Ni at room temperature and 0.24 MPa H_2 was complete in an hour, 89% of the theoretical quantity of hydrogen (reaction **I**, Scheme 9.21) was absorbed and an 83% yield of crude diphenylamine was obtained. In a hydrogenation using a somewhat more dilute solution containing in addition 5 vol% of acetic acid, 85% of the theoretical amount of hydrogen was absorbed and treatment of the solution with sodium hydroxide yielded ammonia equivalent to a 92% reduction. Similar results were also obtained using Adams platinum oxide as catalyst. Thus, it appears that the hydrogenation of *N*-nitrosodiphenylamine over Raney Ni and platinum oxide proceeded by the pathway shown in reaction **I**, although no *unsym*-diphenylhydrazine was found in the reaction mixture.

Ready catalytic hydrogenolysis of *N*-nitrosoamines was utilized by Lorz and Baltzly in removing the nitroso group from *N*-nitroso-*N*-butyl-*p*-anisidine to prepare *N*-butyl-*p*-anisidine.[205] The hydrogenation was performed in methanol over Raney Ni. Adams platinum and Pd–C catalysts were inefficient, both with and without added acetic acid. Harfenist and Magnien also removed the *N*-nitroso group, used in protecting one of the two nitrogens of substituted piperazines, by hydrogenolysis over Raney Ni in methanol (eq. 9.72).[206]



(9.72)

From interest in *N,N*-dimethylhydrazine as a superior fuel for missile and rocket engines, considerable studies have focused on the production of *unsym*-dialkylhydrazines by catalytic hydrogenation of *N*-nitrosodialkylamines.[207–210] Klager et al. studied the hydrogenation of *N*-nitrosodimethylamine (NDMA) in aqueous solution using 10% Pd–C as catalyst, which was found to be much more active than 5% Pd–$CaCO_3$.[209] Low concentrations of both the catalyst and NDMA as well as a low reaction temperature were favorable for increasing yields of *N,N*-dimethylhydrazine. At concentrations of 0.5–4.0 g of 10% Pd–C per 50-ml solution, there was a pronounced decrease in yield of the hydrazine with increasing catalyst concentration. In a run at a very low catalyst concentration, a maximum yield of 86% was obtained. The rate of hydrogenation was essentially independent of the concentration of NDMA. At higher concentrations of both the catalyst (e.g., 1 g per 50-ml solution) and the substrate (e.g., 30% aqueous solution), the rate decreased as the reaction progressed and gas analysis showed the presence of a considerable amount (40–55%) of nitrogen. The normal rate was recovered by replacing the gas with pure hydrogen. Only small quantities of nitrogen were noted over more dilute NDMA solutions. In line with the effect of evolved nitrogen, the rate was approximately proportional to the square of its pressure in the low-pressure range around 1 atm. The yield of the hydrazine decreased almost linearly with increasing reaction temperature from 83% at 1°C to 6% at 63°C. Dimethylamine was isolated as the major product by increasing alkalinity of the reaction mixture. However, no significant quantities of ammonia were found. Tetramethyltetrazene was isolated and identified as the picrate and methiodide. These results, along with the formation of nitrogen, supported the explanation of amine formation proposed by Paal and Yao (reaction **II** in Scheme 9.21).

Smith and Thatcher found that the hydrogenation of *N*-nitrosoamines to the corresponding hydrazines was favored by the addition of an inorganic or organic salt over Pd–C and Pt–C catalysts and, although less markedly, over Rh–C catalyst as well.[210] With Raney Ni, however, the major product obtained was the corresponding amine even in the presence of a salt. In the absence of an added salt, the hydrogenation of *N*-nitrosodiethylamine over 10% Pd–C in 50% aqueous methanol at 60°C and 0.34 MPa H_2 gave a 60% conversion to the corresponding hydrazine and a ratio of the hydrazine to a total base equal to 0.67. On the other hand, by adding calcium chloride (7.5 g per 150 ml 50% aqueous methanol), conversions to the hydrazine as high as nearly 90% and hydrazine:total base ratios greater than 0.9 were achieved (eq. 9.73). Similar effects were obtained by addition of lithium chloride, lanthanum chloride heptahydrate, magnesium sulfate, ammonium acetate, and tetramethylammonium bromide.

$$\underset{20.4\text{ g (0.2 mol)}}{Et_2NNO} \xrightarrow[\substack{150\text{ ml 50\% aq. MeOH/7.5 g }CaCl_2\\ 60^\circ\text{C, 0.34 MPa }H_2\text{, 2.25 h}}]{2.0\text{ g 10\% Pd–C}} \underset{89.0\%\text{ conversion}}{Et_2NNH_2} \qquad (9.73)$$

Although the effect of added salt was less pronounced with 5% Rh–C, the highest conversion of 76% to *N,N*-dimethylhydrazine was obtained in the presence of added calcium chloride, compared to 62% in the absence of an added salt. In general, the palladium catalyst was favored over the rhodium catalyst for higher conversion to the hydrazines. However, a much higher amount of catalyst than with rhodium was required to achieve a reasonable rate with the palladium catalyst. In regard to reaction temperature, best results were obtained at 25 to 30°C with the rhodium catalyst, and at 45–60°C with 10% Pd–C. Over the rhodium catalyst, the hydrogenolysis of *N,N*-dimethylhydrazine to dimethylamine occurred rather readily at higher temperatures and/or increased with prolonged reaction periods. In contrast, the hydrazine was found to be stable and not hydrogenated further under the conditions employed for 10% Pd–C, thus indicating that the dimethylamine formed over Pd–C was derived not through the hydrazine but through another reaction path (see Scheme 9.21). With the palladium catalyst, only a slight increase in conversion to the hydrazine and the rate of hydrogenation was observed between 0.34 and 6.9 MPa hydrogen pressure, while higher hydrogen pressures (6.9 MPa) were favorable significant with rhodium for the rate of reaction and percent conversion to the hydrazine.

Although the way in which the salts affected the reaction was not known, a probable explanation suggested by Smith and Thatcher is that the presence of the salts increases the polar character of the reaction medium, which may increase the polarity of the nitrosamine, and thus the rate of reaction leading to the hydrazine is enhanced by the increase in the polar nature of the substrate. The applicability of this hydrogenation method was also tested with various other nitrosamines. The results are summarized in Table 9.9. It is seen that the conversions to hydrazines are greatly influenced by increasing substitution at the carbon alpha to the nitrosamine group, probably as a result of steric reasons. *N*-Nitrosodiisopropylamine was extremely difficult to hydrogenate to either the hydrazine or the amine. There is also a report that the hydrogenation of *N*-nitroso-3-methyl-2-phenylmorpholine to the corresponding hydrazine was unsuccessful, although it was attempted with a variety of catalysts including Pd–C at room temperature and hydrogen pressures up to 13 MPa in various solvents including ethanol and aqueous ethanol. In every instance, the major product of the hydrogenation was 3-methyl-2-phenylmorpholine.[211] The desired hydrazine was obtained in 95% yield by reduction with lithium aluminum hydride in ethyl ether.

The presence of ferrous salts[212] or ferrous salts with hydroxide ion[213] was also claimed to improve the yields of hydrazines. The shortest reaction time and largest conversion to *N,N*-dimethylhydrazine was obtained in the presence of 0.5 mmol of ferrous sulfate in the hydrogenation of 15 ml of *N*-nitrosodimethylamine over 1 g 5% Pd–C in 135 ml of water at 45°C and 0.28–0.34 MPa H_2.[212] Under similar conditions, 5% Pd–C containing 5 mmol of sodium hydroxide and 1 mmol of ferrous sulfate per gram of catalyst gave 50% reaction in 57 min, 98.9% *N,N*-dimethylhydrazine, and a ratio of 41 moles of the hydrazine per mole of amine.[213]

TABLE 9.9 Hydrogenation of Various N-Nitrosamines in the Presence of Salt[a]

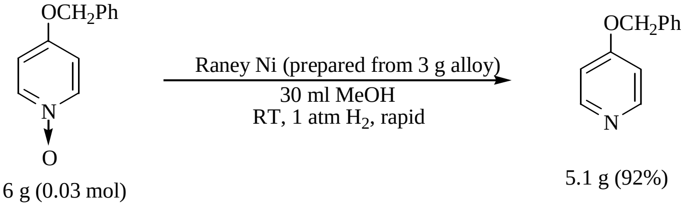
		Solvent (ml)						
Nitrosamine (mol)	Added Salt (g)	95% EtOH	H_2O	Catalyst (g)	T (°C)	Initial H_2 P (MPa)	Time (h)	Conversion to Hydrazine (%)[b]
Diisopropyl- (0.1)	LiCl (15)	70 (MeOH)	0	10% Pd–C (2.0)	44–64	6.2	7	2.6
N-Nitrosomorpholine (0.2)	$CaCl_2$ (30)	0	150	10% Pd–C (2.0)	60	0.35	22.5	82.7
N,*N*′-Dinitrosopiperazine (0.05)	$CaCl_2$ (5)	25	25	10% Pd–C (2.0)	60	6.9	2.75	Quantitative
Diisobutyl- (0.05)	$CaCl_2$ (5)	0	50	10% Pd–C (1.0)	55–75	6.9	2.0	20.3
Diethanol- (0.05)	$CaCl_2$ (1.5)	0	50	10% Pd–C (0.5)	30–70	6.9	2.0	72.5
Dicyclohexyl- (0.05)	$CaCl_2$ (10)	40	20	5% Rh–C (1.0)	80	6.9	5	49.8

[a]Data of Smith, G. W.; Thatcher, D. N. *Ind. Eng. Chem. Prod. Res. Dev*. **1962**, *1*, 117. Reprinted with permission from American Chemical Society.
[b]Determined by oxidation titrations using potassium iodate.

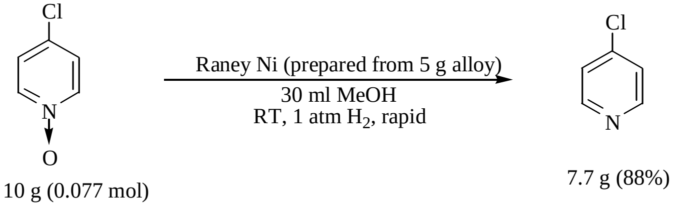
9.5 *N*-OXIDES

N-Heterocyclic aromatic compounds such as pyridines and quinolines can be converted into their *N*-oxides by oxidation with hydrogen peroxide or peracid. Pyridine *N*-oxides are reactive not only toward electrophilic substitution but also toward nucleophilic substitution, and, unlike pyridine, may be substituted preferentially at the 2 and 4 positions.[214] Since the *N*-oxides can readily be reduced to reproduce the parent bases, various 2- and 4-substituted pyridines and quinolines, as well as other substituted *N*-heterocyclic bases, have been prepared through their *N*-oxides.

The hydrogenation of pyridine *N*-oxides to pyridines can readily be carried out over Raney Ni as well as over platinum metal catalysts under mild conditions. Ishii hydrogenated 4-substituted pyridine and quinoline *N*-oxides over Raney Ni in alcohol at elevated temperatures and pressures.[215,216] Under these conditions, however, overhydrogenation to a mixture of tetrahydro derivatives took place with the *N*-oxides of quinoline.[216] Hayashi and co-workers have shown that Raney Ni is sufficiently active under ordinary conditions and more selective than Pd–C in the hydrogenation of *N*-oxides of various heterocyclic aromatic amines.[217–222] In contrast to the hydrogenation over Pd–C, the *N*-oxide group was shown to be preferentially hydrogenated in presence of other substituents such as 4-benzyloxy (eq. 9.74),[219] 4-chloro (eq. 9.75),[217] 4,4′-azo,[222] and 2-styryl groups.[222]

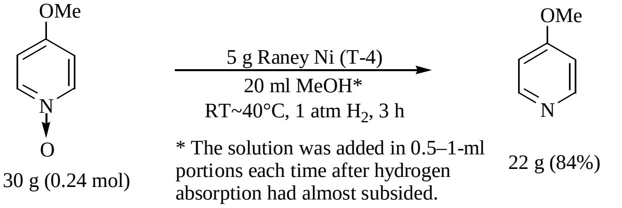


(9.74)



(9.75)

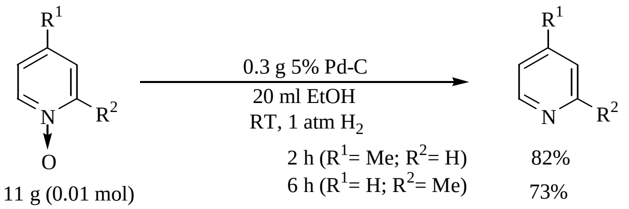
Hydrogenation of the *N*-oxides over Raney Ni proceeds very rapidly, and, since it is a highly exothermic reaction, it is often needed to control the temperature, especially with an active Raney Ni, as demonstrated in the following example:[223]



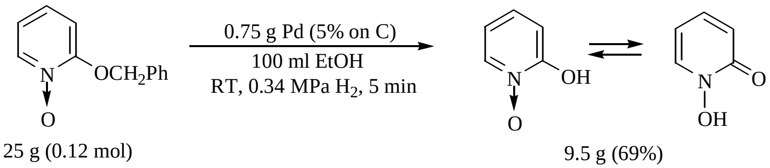
(9.76)

Rylander and Rakoncza compared the rates of hydrogenation of pyridine *N*-oxide over 5% palladium-, platinum-, rhodium-, and ruthenium-on-carbon in methanol, water, and acetic acid.[224] Rhodium was always the most active, although the pyridine ring was hydrogenated concomitantly with the reduction of the *N*-oxide group.

Various *N*-oxides have been hydrogenated over Pd–C as catalyst.[225] According to Katritzky and Monro, 3- and 4-substituted pyridine *N*-oxides are smoothly hydrogenated to pyridines over palladium.[225] 2-Substituted pyridine *N*-oxides, however, are hydrogenated more slowly, except for the 2-phenyl compound, than the corresponding 4-substituted compound, as seen in an example shown in eq. 9.77.[225] In contrast to the hydrogenation with Raney Ni, 2- and 4-benzyloxy groups,[226,227] conjugated C–C double bonds at the 3- and 4-positions,[225] 4-chloro,[225] and 4,4′-azo group[222] are hydrogenated preferentially in the presence of the *N*-oxide group. Thus, 2- (eq. 9.78)[227] and 4-benzyloxypyridine *N*-oxide[226] are hydrogenated over Pd–C to give the corresponding hydroxypyridine *N*-oxides or *N*-hydroxypyridones.



(9.77)



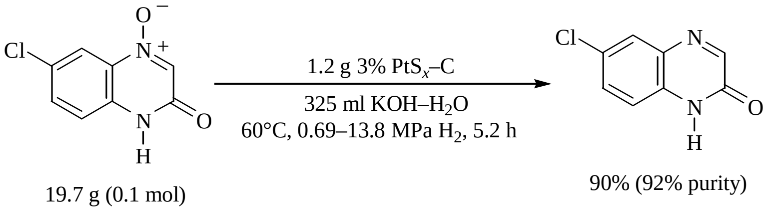
(9.78)

The *N*-oxides of 2- and 4-styrylpyridine and of 3- and 4-pyridineacrylic esters, amides, and acids were hydrogenated to the corresponding saturated pyridine *N*-oxides when the hydrogenations were interrupted after uptake of 1 mol of hydrogen. Further hydrogenation gave the corresponding pyridines, except in the case of 2-styrylpyridine *N*-oxide, where the second mole of hydrogen was absorbed only very slowly.[225] Similar different selectivities between Raney Ni and Pd–C were also observed in the hydrogenation of quinoline and pyrimidine *N*-oxides.[218,221,228] However, 3- and 4-acetylpyridine *N*-oxides were hydrogenated at the oxide group before hydrogenation of the acetyl group took place.[225]

Mitsui et al. studied the selectivity of transition metal catalysts in the hydrogenation of various pyridine *N*-oxides in ethanol at room temperature and atmospheric pressure with Raney Ni, Pd–C, Pt–C, Rh–C, and Ru–C, and at elevated temperatures and pressures with Raney Co, Raney Cu, and copper–chromium oxide.[229] The *N*-oxide groups of 4-benzyloxy- and 4-styrylpyridines were hydrogenated in preference to the other functional groups over Raney Cu, copper–chromium oxide, Raney Co, and Ru–C, similarly as over Raney Ni. Pt–C and Rh–C also showed similar selectivity in

the hydrogenation of 4-benzyloxy derivative; however, in the hydrogenation of the 4-styryl derivative, hydrogenation of the C–C double bond and *N*-oxide group occurred concurrently. The same difference in selectivity between Raney Ni and Pd–C was also observed in the hydrogenation of 2-benzyloxy- and 2-acetoxymethylpyridine *N*-oxides. When a freshly prepared Raney Ni was used, however, a considerable portion of the C–C double bond of 2-styrylpyridine *N*-oxide was found to be hydrogenated in preference to the *N*-oxide group.[228] On the other hand, when Raney Ni, which had been aged for 20 days, was used, the formation of 2-phenethylpyridine *N*-oxide was depressed and preferential hydrogenation of the *N*-oxide group occurred in high selectivity. In contrast to 4-styrylquinoline *N*-oxide, 2-styrylquinoline *N*-oxide was hydrogenated preferentially at the C–C double bond over both Raney Ni and Pd–C.[228]

Malz, Jr. et al. found platinum sulfide supported on carbon to be superior to any of other nonsulfided and sulfided catalysts in the selective hydrogenation of 6-chloro-2(1*H*)-quinoxalinone-4-oxide to 6-chloro-2(1*H*)-quinoxalinone.[230] The hydrogenation was performed in an aqueous potassium hydroxide solution at 60°C and 0.69–1.38 MPa H_2 to give the product containing 92% of the desired compound in 90% isolated yield (eq. 9.79).



(9.79)

9.6 OTHER NITROGEN FUNCTIONS LEADING TO THE FORMATION OF AMINO GROUPS

9.6.1 Azo Compounds

Hydrogenation of azo compounds to amines proceeds stepwise through hydrazo compounds as intermediates. Usually, the hydrogenolysis of hydrazo compounds to give amines is slower than the hydrogenation of azo to hydrazo compounds. However, the relative rate of the hydrogenation to the hydrogenolysis appears to depend greatly on catalyst, substrate, and solvent, as well as on other reaction conditions. Skita observed that hydrogenation of azobenzene (9.1 g) to hydrazobenzene was very rapid and the theoretical amount of hydrogen was absorbed in 5 min, but further hydrogenation to aniline was much slower and completed in 4.5 h, over a colloidal palladium (Skita) (0.03 g Pd) in ethanol (250 ml) at room temperature and 2 atm of hydrogen.[231] Ashley and Berg obtained 4,4′-dicyanohydrazobenzene in 80% yield in the hydrogenation of 4,4′-dicyanoazoxybenzene or 4,4′-dicyanoazobenzene over 10% Pd–C in dioxane at room temperature and just above 1 atm. H_2.[232]

Rylander and Karpenko studied the rates of hydrogenation and subsequent hydrogenolysis of azobenzene in ethanol and in acetic acid and of *p*-phenylazoaniline in acetic acid over three platinum metal-on-carbon catalysts at room temperature and atmospheric pressure.[233] The results in Table 9.10 show that the hydrogenation of azobenzene as well as the hydrogenolysis of hydrazobenzene are much faster in acetic acid than in ethanol. The rates were the greatest and the relative rate ratio of the hydrogenation to the hydrogenolysis was smallest with Pd–C in acetic acid. In contrast, hydrogenation of *p*-phenylazoaniline proceeded at a constant rate until 2 mol of hydrogen had been absorbed, although the selectivity at half-hydrogenation was not investigated.

Similar to the cases with platinum metals, the rate of hydrogenolysis of hydrazobenzene appears to be smaller than that of azobenzene over Raney Ni as well,[234] although Wisniak and Klein observed the formation of only azoxy- and azobenzenes, and no hydrazobenzene, during the course of hydrogenation of nitrobenzene over Raney Ni at 170°C and 1.38 MPa H_2.[235]

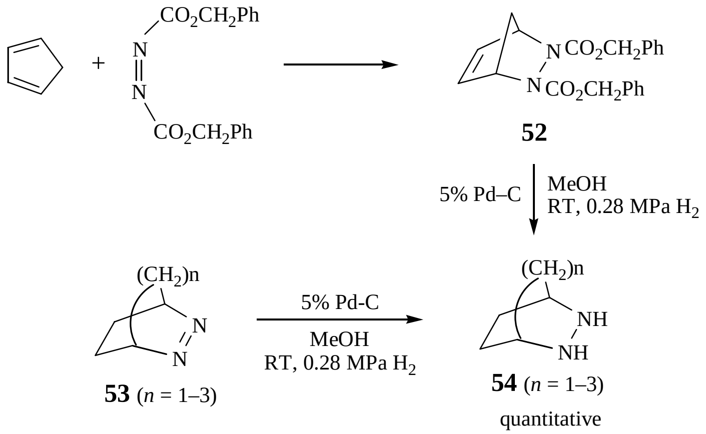
The N–N bond in aliphatic hydrazo compounds appears to be more resistant to hydrogenolysis than in the corresponding aromatic compounds. The adduct of cyclopentadiene and dibenzyl azodicarboxylate **52** was hydrogenated smoothly over 5% Pd–C in methanol to provide 2,3-diazabicycloheptane (**54**, n = 1) in quantitative yield. No secondary N–N bond cleavage of the hydrazine was observed under these conditions. The hydrogenation of bicyclic azo alkanes **53** (n = 1–3) under the same conditions also gave the corresponding hydrazines quantitatively (Scheme 9.22).[236]

Catalytic hydrogenation of aromatic azo compounds, usually obtained by diazo coupling, to amines provides a useful method for introducing an amino group into carbocyclic or heterocyclic aromatic rings. Palladium, platinum, and Raney Ni have been employed successfully for this hydrogenation at low temperatures and pressures. In most cases azo compounds were hydrogenated in suspended state in solvent at the starting. Examples are shown in eqs. 9.80–9.83.[237–240]

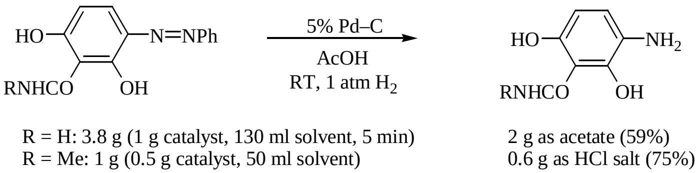
TABLE 9.10 Rates of Hydrogenation (ml H_2/min/0.1 g catalyst) of Azobenzenes[a,b]

	Azobenzene				*p*-Phenylazoaniline AcOH Solvent	
	EtOH Solvent		AcOH Solvent			
Catalyst	1st mol H_2	2nd mol H_2	1st mol H_2	2nd mol H_2	1st mol H_2	2nd mol H_2
5% Pd–C	11	2	100	45	95	95
5% Pt–C	19	1	47	5	30	30
5% Rh–C	15	>1	30	3	40	40

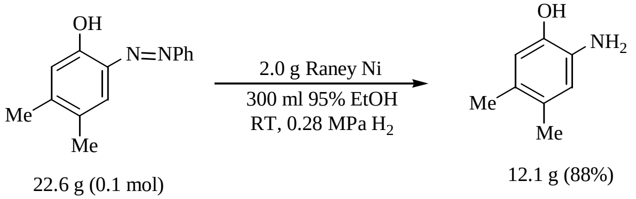
[a]Data of Rylander, P. N.; Karpenko, I. in Rylander, P. N. *Catalytic Hydrogenation over Platinum Metals*; Academic Press: New York, 1967; p 493. Reprinted with permission from Academic Press Inc.
[b]Hydrogenations were carried out with 0.1 g catalyst and 2.0 g azobenzene or *p*-phenylazoaniline in 50 ml of solvent at room temperature and atmospheric pressure.



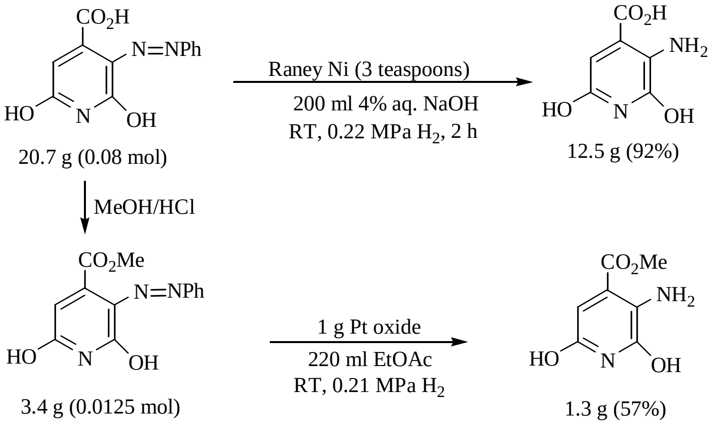
Scheme 9.22 Hydrogenation of bicyclic azoalkanes over Pd–C.



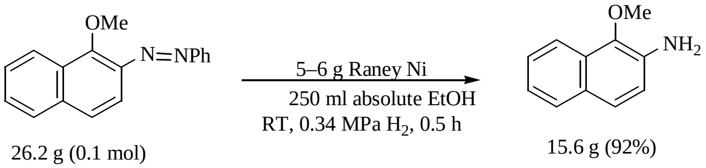
(9.80)



(9.81)

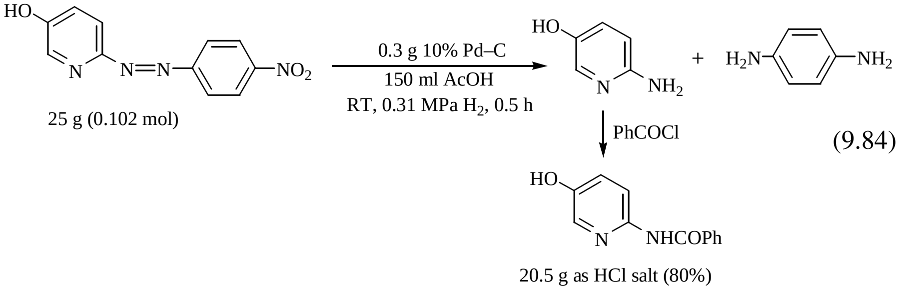


(9.82)



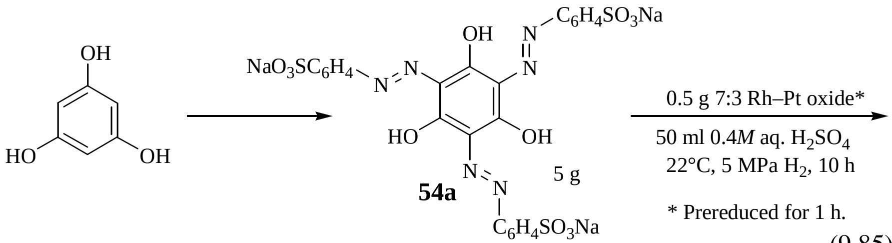
(9.83)

Hydrogenation of diazo coupling products of 3-hydroxypyridines has been shown to be a useful method for the preparation of 2-amino-5-hydroxypyridines. The synthesis was carried out with *p*-nitrobenzeneazo derivatives that were hydrogenated over Pd–C in acetic acid, as in the following example:[241]

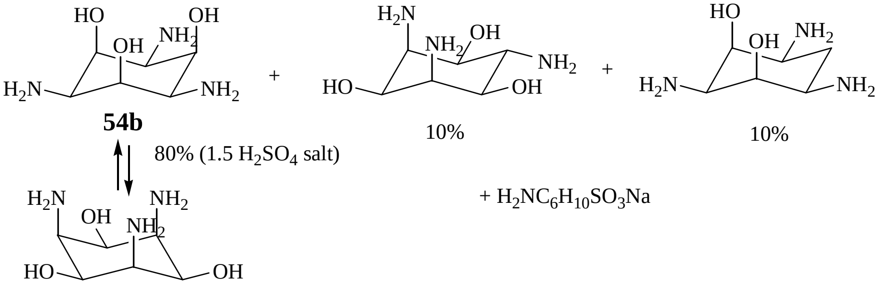


(9.84)

Ghisletta et al. studied a new, convenient, and safe route to 1,3,5-triamino-1,3,5-trideoxy-*cis*-inositol (**54b**) by hydrogenation of azo-coupled derivatives of phloroglucinol.[242] In the presence of acetic anhydride, the hydrogenation of tris(phenylazo)phloroglucinol over 5% Pd–C resulted in the formation of tri-, hexa-, and nonaacetylated derivatives of triaminophloroglucinol. However, further hydrogenation to the cyclohexane derivatives was unsuccessful. Hydrogenation to the cyclohexane derivative could be achieved by a one-pot hydrogenation of the water-soluble trisodiumtris(*p*-sulfonatophenylazo)phloroglucinol (**54a**) in a dilute sulfuric acid at 22°C and 5 MPa H_2, using prereduced Nishimura rhodium–platinum oxide catalyst, which had been found to be the most effective among various unsupported and supported catalysts investigated in activity as well as in selectivity to the *cis*-triaminocyclitol **54b** (eq. 9.85).

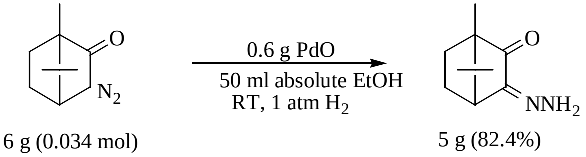


(9.85)



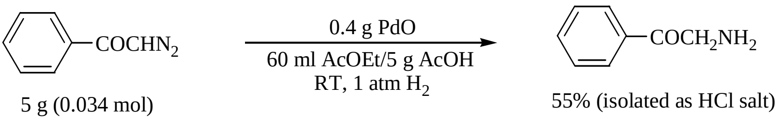
9.6.2 Diazo Compounds

Simple diazoalkanes usually lose nitrogen on catalytic hydrogenation to give hydrocarbons. Even diaryldiazomethane and diazoacetic acid ester are hydrogenated to give diarylmethane and acetic acid ester, respectively.[243] Birkofer studied the behavior of various diazoketones over palladium oxide at room temperature and atmospheric pressure.[243] Diazoketones with aliphatic or alicyclic chains are hydrogenated mainly to the corresponding hydrazones without formation of ammonia. Thus, isovaleryldiazomethane was hydrogenated to isobutylglyoxal monohydrazone; and diazocamphor, to camphorquinone monohydrazone (eq. 9.86).

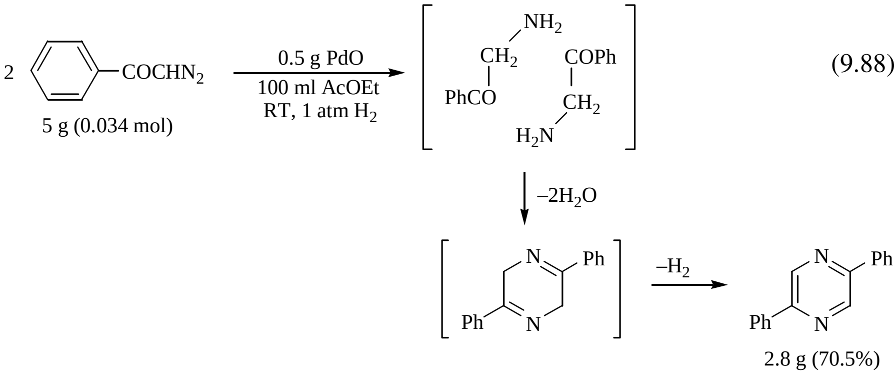


(9.86)

Hydrogenation of phenyl- or benzyl-substituted diazoketones affords the corresponding aminoketones, which may undergo further transformation. ω-Dioazoacetophenone was hydrogenated to ω-aminoacetophenone and ammonia in ethyl acetate containing acetic acid (eq. 9.87). In the absence of acetic acid, however, 2,5-diphenylpyrazine was obtained in good yield (eq. 9.88). Hydrogenation in the presence of hydrochloric acid led to the formation of acetophenone with evolution of nitrogen.

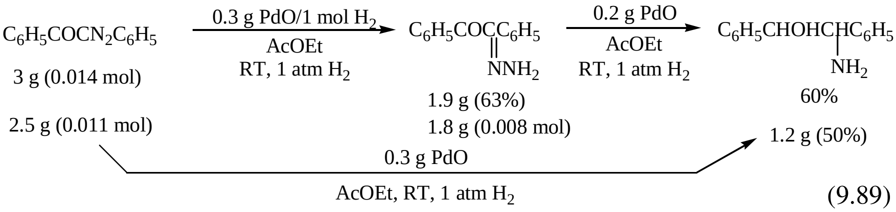


(9.87)



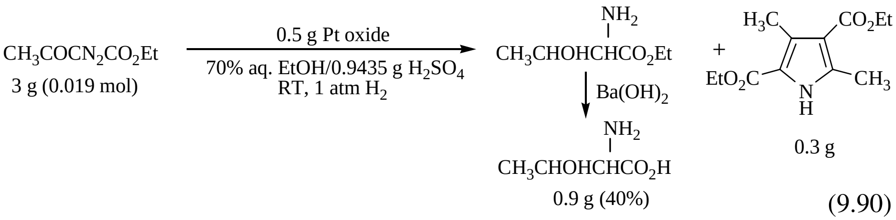
(9.88)

Benzoylphenyldiazomethane was hydrogenated to 1,2-diphenylaminoethanol in ethyl acetate, but with uptake of 1 mol of hydrogen the intermediate benzil monohydrazone could be isolated in good yield (eq. 9.89). Hydrogenation of the hydrazone under the same conditions gave 1,2-diphenylaminoethanol in 60% yield.



(9.89)

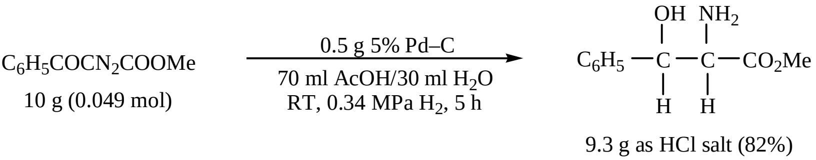
A mixture of DL-threonine and DL-allothreonine was prepared by the hydrogenation of ethyl diazoacetoacetate over paltinum oxide in 70% ethanol containing sulfuric acid (eq. 9.90). 2,4-Dimethylpyrrole-3,5-dicarboxylic acid diethyl ester was also obtained as a byproduct.



(9.90)

Looker and Thatcher synthesized allophenylserine (DL-*erythro*-β-phenylserine) in high yield by hydrogenation of methyl benzoyldiazoacetate over 5% Pd–C in 70% acetic acid (eq. 9.91).[244] The hydrogenation was highly stereospecific, and the allophenylserine obtained did not reveal any of the diasteromeric *threo* form. The same reduction by a variety of chemical reducing agents led either to recovery of the starting

diazo compound or, in the case of aluminum amalgam, to a complex mixture of products.



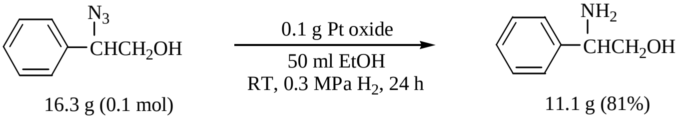
(9.91)

9.6.3 Azides

The hydrogenation of azides has been applied to introducing a primary amino group, starting with those compounds that are susceptible to nucleophilic attack by an alkali metal azide, such as haloalkanes, epoxides, and aziridines. Since nucelophilic attack by an azide anion proceeds with inversion of configuration [an S_N2 (bimolecular nucleophilic substition) mechanism] and the resulting organic azide is hydrogenated to the corresponding amine with retention of configuration, the hydrogenation of azides may provide a useful method for the stereoselective synthesis of amino compounds. The hydrogenation is usually carried out under mild conditions with the use of palladium, platinum, or Raney Ni as catalyst. The hydrogenation, however, cannot be traced by the uptake of hydrogen, since 1 mol of nitrogen is evolved for the uptake of 1 mol of hydrogen, which is required for reducing an azide to the amine (eq. 9.92).

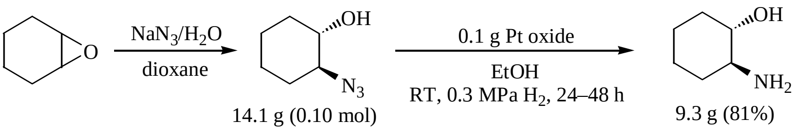
$$RN_3 + H_2 \longrightarrow RNH_2 + N_2 \qquad (9.92)$$

McEwen et al. hydrogenated 2-azido-2-phenylethanol, prepared by the reaction of styrene oxide with sodium azide, over platinum oxide in ethanol to give 2-amino-2-phenylethanol in 81% yield (eq. 9.93).[245]

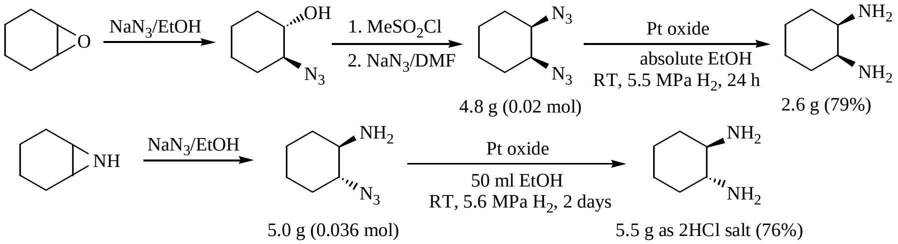


(9.93)

The reaction of the epoxides of cyclopentene and cyclohexene with sodium azide give the *trans*-azido alcohols, the hydrogenation of which affords the *trans* isomers of 2-aminocyclopentanol and 2-aminocyclohaexanol (eq. 9.94) stereospecifically.[246] By using these reactions, Swift and Swern prepared stereochemically pure *cis*- and *trans*-1,2-diaminocyclohexanes by the reaction sequences described in Scheme 9.23.[247]

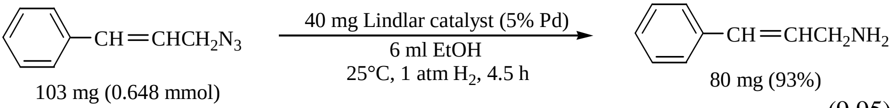


(9.94)

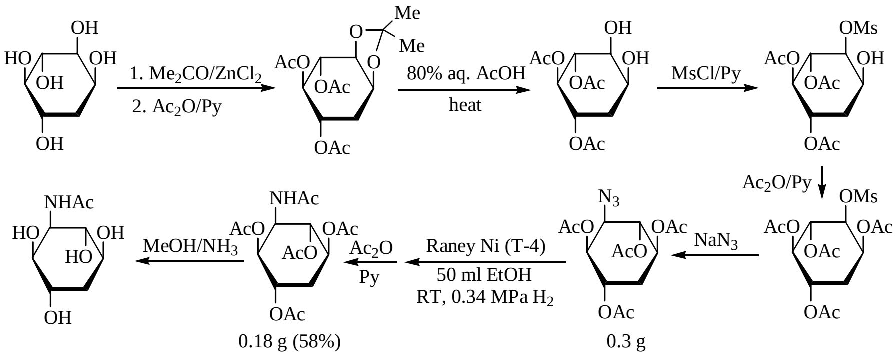


Scheme 9.23 Stereospecific synthesis of *cis*- and *trans*-1,2-diaminocyclohexanes.

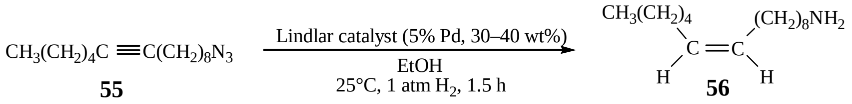
The hydrogenation of azides has been applied by Suami and co-workers to the synthesis of various aminocyclitols.[248–250] The hydrogenation was usually carried out over platinum oxide or Raney Ni in ethanol. An example using Raney Ni is shown in the reaction sequence outlined in Scheme 9.24.[248] Corey et al. demonstrated that selective transformation of the azide to primary amine in the presence of C–C double bonds and carbonyl groups could be effectuated by hydrogenation with Lindlar catalyst (5% Pd) in ethanol at 25°C and atmospheric pressure of hydrogen.[251] As a typical example, cinnamyl azide, obtained from cinnamyl bromide and lithium azide, was hydrogenated to cinnamylamine in 93% yield over Lindlar catalyst in ethanol (eq. 9.95). In the case of acetylenic azide **55**, the rates of hydrogenation of the azide and acetylenic functions were approximately the same and the *cis*-olefinic amine **56** was produced in 95% yield (eq. 9.96).



(9.95)



Scheme 9.24 Synthesis of *N*-acetyl-1-deoxy-*muco*-4-inosamine from 1-deoxy-*myo*-inositol.



(9.96)

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CHAPTER 10

Hydrogenation of Carboxylic Acids, Esters, and Related Compounds

10.1 CARBOXYLIC ACIDS

In general, carboxylic acids are hydrogenated with difficulty under mild conditions over usual metallic catalysts. However, it has been recognized that acetic acid may be reduced over platinum oxide under very mild conditions in the presence of perchloric acid.[1] Kaplan observed that acetic acid was reduced rapidly over rhodium catalysts at room temperature and pressure, but the reduction stopped abruptly after a very small conversion.[2] The occurrence of these reductions may lead to appreciable errors in the amounts of absorbed hydrogen when hydrogenations are carried out in acetic acid as solvent, although the reductions usually proceed only to limited extents, probably due to formation of some poisonous products. These undesired reductions of acetic acid solvent may be depressed in the presence of a substrate that may be adsorbed more strongly than acetic acid.

10.1.1 Hydrogenation to Alcohols

Carboxylic acids are hydrogenated to the corresponding alcohols at high temperatures and pressures over catalysts such as copper, rhodium, ruthenium, and rhenium. Schrauth et al. hydrogenated fatty acids, such as lauric and stearic acids, to the corresponding alcohols at 320–340°C and to hydrocarbons at 350–390°C over supported copper catalysts under high hydrogen pressures.[3,4] Guyer et al. studied the hydrogenation of aliphatic carboxylic acids with 4–12 carbon atoms over copper–chromium oxide and copper oxide as catalysts at 300°C under 25 MPa H_2.[5] At temperatures lower than 300°C the hydrogenation was incomplete, but above 300°C further hydrogenation to give hydrocarbons took place. As seen from the results shown in Table 10.1, the lower carboxylic acids with less than 4 carbon atoms were hydrogenated only to small extents or practically not hydrogenated, probably because these acids with stronger acidity might dissolve and hence deactivate the catalysts. Over copper–chromium oxide satisfactory yields of alcohols were obtained only with the carboxylic acids containing 10–12 carbon atoms, while over copper oxide the carboxylic acids with more than 7 carbon atoms gave good yields of alcohols. Significant increase in the yield of alcohols was not obtained with addition of CaO, BaO, or MgO to copper oxide (7% increase in the case of heptanoic acid). Similar results were also obtained with aliphatic dicarboxylic acids with 4–21 carbon atoms (Table 10.2).[6] Over Cu–Ba–Cr oxide, instances where a good yield of the corresponding glycol was obtained

TABLE 10.1 Hydrogenation of Fatty Acids to Alcohols over Copper Catalysts[a,b]

	Composition of reaction mixture (%)					
	Cu–Cr oxide			Cu oxide		
Carboxylic acid	Alcohol	Ester	Acid	Alcohol	Ester	Acid
$CH_3(CH_2)_{10}CO_2H$	91.3	6.2	0.25	94.0	1.6	0.1
$CH_3(CH_2)_9CO_2H$	88.0	10.7	0.35	92.8	6.3	0.2
$CH_3(CH_2)_8CO_2H$	79.4	15.5	0.3	83.6	16.3	0.2
$CH_3(CH_2)_7CO_2H$	37.6	55.0	5.2	77.2	18.9	1.6
$CH_3(CH_2)_6CO_2H$	20.3	61.6	16.3	83.5	15.2	0.8
$CH_3(CH_2)_5CO_2H$	6.9	50.1	33.1	77.0	22.3	1.0
$CH_3(CH_2)_4CO_2H$	5.9	55.5	34.7	40.6	51.0	7.8
$CH_3(CH_2)_3CO_2H$	4.2	44.9	43.9	11.4	71.6	9.8
$CH_3(CH_2)_2CO_2H$	0.1	27.2	61.9	10.9	53.1	29.2

[a]Data of Guyer, A.; Bieler, A.; Jaberg, K. *Helv. Chim. Acta* **1947**, *30*, 39. Reprinted with permission from Verlag Helvetica Chimica Acta AG.
[b]The carboxylic acid was hydrogenated over 5 wt% of catalyst under 25 MPa H_2 at 300°C for 1.5 h.

TABLE 10.2 Hydrogenation of Dicarboxylic Acids to Glycols over Copper Catalysts[a]

	Composition of Reaction Mixture (mol%)					
	Cu–Cr–Ba Oxide[b]		Cu–Cr–Ba Oxide[c]		Cu Oxide[b]	
Dicarboxylic Acid	Glycol	Ester	Glycol	Ester	Glycol	Ester
$HO_2C(CH_2)_2CO_2H$	—	—	11.0	87.0	0	23.0
$HO_2C(CH_2)_3CO_2H$	—	—	47.0	51.0	0	43.0
$HO_2C(CH_2)_4CO_2H$	—	—	90.0	9.5	0	78.0
$HO_2C(CH_2)_5CO_2H$	—	—	—	—	65.0	32.5
$HO_2C(CH_2)_6CO_2H$	0	62.0	—	—	76.0	22.0
$HO_2C(CH_2)_7CO_2H$	0	95.0	—	—	82.5	17.0
$HO_2C(CH_2)_8CO_2H$	7.5	92.0	92.5	7.0	83.5	16.5
$HO_2C(CH_2)_9CO_2H$	10.0	90.5	—	—	84.0	15.0
$HO_2C(CH_2)_{10}CO_2H$	17.0	81.0	—	—	86.0	13.0
$HO_2C(CH_2)_{11}CO_2H$	41.0	56.0	—	—	90.5	9.0
$HO_2C(CH_2)_{16}CO_2H$	94.5	5.0	—	—	—	—
$HO_2C(CH_2)_{19}CO_2H$	97.5	2.0	—	—	99.5	0

[a]Data of Guyer, A.; Bieler, A.; Sommaruga, M. *Helv. Chim. Acta* **1955**, *38*, 976. Reprinted with permission from Verlag Helvetica Chimica Acta AG.
[b]The dicarboxylic acid (10 g) was hydrogenated over 5–9 wt% of catalyst under 27 MPa of maximum H_2 pressure at 280–300°C for 6 h.
[c]The 40-ml dioxane solution containing 3 g of dicarboxylic acid was subjected to hydrogenation under 28 MPa of maximum H_2 pressure at 260–290°C for 12 h.

were limited to the acids with more than 13 carbon atoms. However, with the use of a solvent such as dioxane, high yields of glycols could be obtained with adipic acid and sebacic acid. Over copper oxide the acids with 7–13 carbon atoms gave good glycol yields.

Grimm et al. have reported that rhodium oxide can hydrogenate fatty acids to the corresponding alcohols in water at 150–175°C and 13.8 MPa H_2.[7] The hydrogenation was accompanied by the formation of large amounts of esters, since esters were inert toward hydrogenation under these reaction conditions. The total yield of nonyl alcohol after the hydrolysis of ester was 49% in 6 h and 63% in 9 h when nonanoic acid (15 g) was hydrogenated over 0.2 g $Rh_2O_3{\cdot}5H_2O$ at 150°C and 13.8 MPa H_2. In the case of benzoic acid, a rapid pressure drop occurred around 75°C, corresponding to saturation of the benzene ring, and the product was a mixture of cyclohexanemethanol, cyclohexylmethyl cyclohexanecarboxylate, and cyclohexanecarboxylic acid.

Carnahan et al. obtained good yields of alcohols and glycols by hydrogenation of lower mono- and dicarboxylic acids over ruthenium dioxide or Ru–C at 135–225°C and 34–69 MPa H_2 (eqs. 10.1 and 10.2).[8] In general, the optimum temperature was about 150°C. The chief side reaction was hydrogenolysis of the alcohols, as exemplified in the formation of ethanol from oxalic acid and of butanol and propanol from succinic acid (see eq. 10.2). Platinum and palladium catalysts were ineffective under similar or even more severe conditions.

$$\underset{\text{120 g (2 mol)}}{CH_3CO_2H} \xrightarrow[\text{147–170°C, 70–95 MPa } H_2\text{, 10 h}]{\text{1.8 g Ru dioxide}} \underset{88\%}{CH_3CH_2OH} \qquad (10.1)$$

$$\underset{\text{118 g (1 mol)}}{HO_2C(CH_2)_2CO_2H} \xrightarrow[\text{152–192°C, 72–95 MPa } H_2\text{, 4–5 h}]{\text{1.8 g Ru dioxide}} HO(CH_2)_4OH\ (59\%) + CH_3(CH_2)_3OH + CH_3(CH_2)_2OH \qquad (10.2)$$

α,ω-Dicarboxylic acids, $HO_2C(CH_2)_nCO_2H$ ($n = 8 - 16$), were hydrogenated to ω-hydroxycarboxylic acids, $HOCH_2(CH_2)_nCO_2H$, over a ruthenium catalyst prepared from $RuCl_3$, $Sn(OEt)_4$, hexyleneglycol, and aluminum isopropoxide.[9] Pentadecanedioic acid was hydrogenated over this catalyst in decalin at 280°C and 9.8 MPa H_2 to give 62.3% ω-hydroxypentadecanoic acid.

Broadbent et al. have found that the rhenium blacks prepared by reducing rhenium heptoxide are highly effective catalysts for the hydrogenation of carboxylic acids to alcohols at 150–170°C for monocarboxylic acids (eq. 10.3) and at 200–250°C for dicarboxylic acids (eq. 10.4) under 13.5–27 MPa H_2.[10,11] Rhenium heptoxide can be reduced to the active blacks in appropriate solvent (ethanol, 1,4-dioxane, acetic acid, or water) at 120–220°C and 15–21 MPa H_2 for 1–2 h, or more conveniently, in situ in

$$\underset{\text{50 g (0.35 mol)}}{C_7H_{15}CO_2H} \xrightarrow[\substack{H_2O\text{ (50 ml)/dioxane} \\ \text{163°C, 19.3 MPa } H_2\text{,* 14 h}}]{\text{1 g } Re_2O_7} \underset{100\%}{C_8H_{17}OH} \qquad (10.3)$$

* Average total pressure at the reaction temperature.

$$\underset{50\ \text{g}\ (0.38\ \text{mol})}{HO_2C(CH_2)_3CO_2H} \xrightarrow[\substack{50\ \text{ml}\ H_2O \\ 250°\text{C},\ 17.9\ \text{MPa}\ H_2,^*\ 50\ \text{h}}]{1\ \text{g}\ Re_2O_7} \underset{100\%}{HO(CH_2)_5OH} \qquad (10.4)$$

* Average total pressure at the reaction temperature.

the presence of the substrate. The ester formation was markedly reduced by hydrogenation in the presence of water. Benzoic acid was overhydrogenated to give toluene in 91% yield at 250°C and 19 MPa H_2, although ethyl benzoate was hydrogenated to benzyl alcohol in 89% yield under similar conditions. Phenylacetic acid was hydrogenated to a mixture of 78% of 2-phenylethanol and 22% of its phenylacetic acid ester without solvent at 149°C and 16 MPa H_2. Succinic acid was hydrogenated to 61% butyrolactone, 33% 1,4-butanediol, and 6% polyesters in dioxane; to 94% 1,4-butanediol and 6% 1-butanol without solvent; and to a mixture of 13% tetrahydrofuran, 59% 1,4-butanediol, and 3% polyesters in water.

Yoshino et al. studied a rhenium–osmium binary system that was found to be effective for the hydrogenation of fatty acids to alcohols under milder conditions than required for rhenium catalysts.[12] The rhenium–osmium catalyst was even more effective than a mixture of Re_2O_7–5% Ru–C, a catalyst system that was found by Trivedi et al. to show a marked synergism in the hydrogenation of octanoic acid (eq. 10.5),[13] although the synergistic effect of rhenium and ruthenium was also confirmed. The most effective catalyst was prepared by reducing a mixture of Re_2O_7 (0.5 g, 2.0 mmol Re) and OsO_4 (1.0 g, 4.0 mmol Os) at 140°C and 10 MPa H_2 for 1 h in ethyl acetate in the presence of succinic acid (0.89 g, 7.5 mmol). Decanoic acid was hydrogenated to decanol in high conversions over this catalyst at 100–120°C and at hydrogen pressure 2.5–10 MPa. Overreduction of decanol to decane, which was even faster than the hydrogenation of decanoic acid to decanol, could be markedly depressed with the addition of a small amount of thiophene. A typical run using this catalyst system is given in eq. 10.6.

$$\underset{28.8\ \text{g}\ (0.20\ \text{mol})}{C_7H_{15}CO_2H} \xrightarrow[\substack{28.8\ \text{g dioxane}/5.0\ \text{g}\ H_2O \\ 170°\text{C},\ 17.2\ \text{MPa}\ H_2,\ 3\ \text{h}}]{0.13\ \text{g}\ Re_2O_7/1.0\ \text{g}\ 5\%\ \text{Ru–C}\ (50\%\ \text{wet})} \underset{\substack{\text{trace} \\ (21.2)^*}}{\text{acid}} + \underset{\substack{84.0 \\ (48.1)^*}}{\text{alcohol}} + \underset{\substack{16.0 \\ (30.7)^*}}{\text{ester}} \qquad (10.5)$$

* Hydrogenation over 0.26 g Re_2O_7 for 6 h.

$$\underset{17.2\ \text{g}\ (0.10\ \text{mol})}{CH_3(CH_2)_8CO_2H} \xrightarrow[\substack{26\ \text{g dioxane}/0.0084\ \text{g}\ (0.1\ \text{mmol})\ \text{thiophene} \\ 100°\text{C},\ 10\ \text{MPa}\ H_2,\ 6.6\ \text{h},\ 94.4\%\ \text{conversion}}]{0.5\ \text{g}\ Re_2O_7\ (2.0\ \text{mmol Re})–1.0\ \text{g}\ OsO_4\ (4.0\ \text{mmol Os})} \begin{array}{l} C_{10}H_{21}OH\ (84.9\%) \\ C_{10}H_{22}\ (8.2\%) \\ \text{ester}\ (1.4\%) \end{array} \qquad (10.6)$$

Novotny found that neat trifluoroacetic acid could be hydrogenated to 2,2,2-trifluoroethanol in the presence of rhodium or iridium catalyst under much milder con-

ditions (50–150°C, 0.4–1.2 MPa H_2)[14] than over rhenium blacks (207°C, 30 MPa H_2)[10] or over a supported ruthenium (> 150°C, 6.9–69 MPa H_2).[15] The rates of hydrogenation at 113°C and 1.12 MPa H_2, as expressed by $k_0 \times 10^5$ mol·min^{-1}·g cat^{-1}, were 7.6 for 5% Rh–C, 0.7 for 5% Rh–Al_2O_3, 3.1 for rhodium black, 7.6 for iridium black, and 9.5 for $Rh_2O_3 \cdot 5H_2O$. Under these conditions, 1.9 g of trifluoroacetic acid was hydrogenated in 2–3 h to give 90% yields of the trifluoroethanol over 0.1 g of 5% supported catalyst or 0.05 g of unsupported catalysts. The rates of hydrogenation of perfluoropropionic acid and perfluorobutyric acid at comparable conditions were about 20 times smaller.

Several catalyst systems have been reported to be effective for the transformation of unsaturated fatty acids and esters to the corresponding unsaturated alcohols.[16–18] Cheah et al. have found that Ru–Sn–Al_2O_3 catalysts selectively hydrogenate oleic acid to 9-octadecen-1-ol at low pressure in high yield.[18] The optimum Ru:Sn atomic ratio was about 1:2. The Ru–Sn catalyst prepared by an improved sol–gel method[19,20] showed higher activity and selectivity than the catalysts prepared by impregnation or coprecipitation methods. Under the optimum reaction conditions (250°C and 5.6 MPa H_2), the selectivities of 80.9 and 97% for 9-octadecen-1-ol and total alcohols (9-octadecenol plus stearyl alcohol), respectively, were obtained at a conversion of 81.3% when 50 g of oleic acid was hydrogenated over 6 wt% of the sol-gel Ru–Sn–Al_2O_3 (2 wt% Ru; 1:2 atomic ratio of Ru:Sn) for 9 h.[18] Re–Sn catalyst system was also effective for the transformation of oleoic acid to the corresponding unsaturated alcohol. The catalyst prepared from ammonium perrhenate and stannic chloride on Al_2O_3 showed the best performance in the transformation of oleic acid to the corresponding unsaturated alcohol (25–36% yields at 60–80% conversion) at 250°C and 5.6 MPa H_2.[21]

10.1.2 Hydrogenation to Aldehydes

The hydrogenation of carboxylic acids to aldehydes has been reported in only a few cases. Since glucose was known not to be reduced in neutral solution in the presence of platinum black,[22] Glattfeld and Shaver studied the hydrogenation of *d*-gluconic acid to *d*-glucose over platinum oxide in neutral or slightly acid solution at room temperature and 0.12–0.069 MPa H_2, and obtained *d*-glucose in 14–28% yield (measured as osazone), when the acid (from 6.2 g of its calcium salt) was hydrogenated with use of a rather large quantity of platinum oxide (by addition of each 1 g portion of platinum oxide three times) for 7.5 h in total.[23] With mannonic acid, however, a yield of only 0–2% of mannose (as osazone) was obtained, while galactonic acid was hydrogenated to dulcitol in 30–45% yield. Subsequently, Glattfeld and Schimpff obtained higher yields of sugars by hydrogenation of the δ-lactones of the corresponding aldonic acids (see eq. 10.31).[24] The γ-lactones gave lower yields of sugars owing to further hydrogenation to the corresponding alcohols.

Maki and Yokoyama have recently developed an effective catalyst system consisting of ZrO_2 and a modifier, such as chromium ion, for vapor-phase hydrogenation of both aliphatic and aromatic carboxylic acids and esters to the corresponding aldehydes.[25–27] The metal ions used as modifiers markedly improved the activity and life of ZrO_2 catalyst. As an example, benzoic acid was hydrogenated to benzaldehyde in

TABLE 10.3 Vapor-Phase Hydrogenation of Carboxylic Acids and Esters to Aldehydes over Modified ZrO_2 Catalyst[a,b]

Carboxylic Acid or Ester	Conversion (%)	Selectivity for Aldehyde (%)
o-Toluic acid	98	97
Diphenyl ether 3-carboxylic acid	97	96
Dimethyl terephthalate	64	73
3-Chlorobenzoic acid	82	77
Pivalic acid	97	99
Methyl caproate	50	70
Cyclohexanecarboxylic acid	95	98
Methyl nicotinate	86	83
Methyl 4-methylthiazole-5-carboxylate	74	80
Furan-3-carboxylic acid	62	52

[a]Data of Maki, T.; Yokoyama, T. *Yuki Gosei Kagaku Kyokaishi* **1991**, *49*, 195. Reprinted with permission from Society of Synthetic Organic Chemistry, Japan.
[b]300–400°C, H_2 space velocity = 1250 h^{-1}, acid/H_2 = 2/98 (%).

98% conversion with 96% selectivity over ZrO_2 modified with chromium at 350°C [H_2 space velocity = 1250 h^{-1}, acid/H_2 = 2/98 (%), Cr/Zr = 5/100 atomic ratio]. The results of the hydrogenation of various other aromatic and aliphatic carboxylic acids and esters over the modified ZrO_2 catalyst are summarized in Table 10.3.[28] Some mechanistic studies on the hydrogenation of methyl benzoate to benzaldehyde have been reported by Aboulayt et al. with ZnO, ZrO_2, CeO_2, and TiO_2 as catalysts at 300 and 350°C and atmospheric pressure.[29]

10.2 ESTERS, LACTONES, AND ACID ANHYDRIDES

10.2.1 Esters

Carboxylic acid esters are hydrogenated to the corresponding alcohols in the presence of suitable catalysts usually at high temperatures and pressures, which, however, depend on the nature and the amount of catalyst as well as the structure of substrate.[4,30,31] Adkins and co-workers found that copper–chromium oxide is an especially effective catalyst for this type of hydrogenation.[32] The hydrogenation of esters to alcohols is a reversible reaction;[5,33] therefore, the relative concentrations of esters and alcohols at equilibrium depend on the temperature and, in particular, on the hydrogen pressure. The concentration of esters at equilibrium was found to be about 1% with diethyl adipate, diethyl glutarate, methyl myristate, and ethyl laurate at 240–260°C and 20–30 MPa H_2. Since the products from these esters at equilibrium might contain rather complex mixtures of esters and alcohols, Adkins and Burks, Jr. have determined the effect of hydrogen pressure on the extent of hydrogenation at 260°C, using octyl caprylate from which only a single ester and alcohol should be formed (Scheme 10.1).[34] Thus, the concentration of the ester varied from 0.9% at 27.4 MPa H_2 to 80.3% at 0.97 MPa

$$C_7H_{15}CO_2C_8H_{17} + 2H_2 \underset{260°C}{\overset{\text{Cu–Cr oxide}}{\rightleftharpoons}} 2\ C_8H_{17}OH$$

Ester at equilibrium (%)	H_2 pressure (MPa)
0.9*	27.4
1.9* (2.5)†	18.6 (20.3)†
2.4*	16.9
5.5* (14.5)†	10.9 (9.5)†
9.7‡	8.3
15.8*	6.4
16.0*	6.3
41.8‡ (39.2)†	3.2 (3.8)†
57.7§	2.2
80.3* (63.8)†	0.97 (1.4)†

* 50 g (0.195 mol) of ester at beginning of reaction.
‡ 50.75 g (0.39 mol) of octanol at beginning of reaction.
§ 20 g (0.078 mol) of ester and 30.45 g (0.234 mol) of octanol at beginning of reaction.
† Reaction at 290°C.

Scheme 10.1 The equilibria of octyl caprylate, octanol, and hydrogen systems.

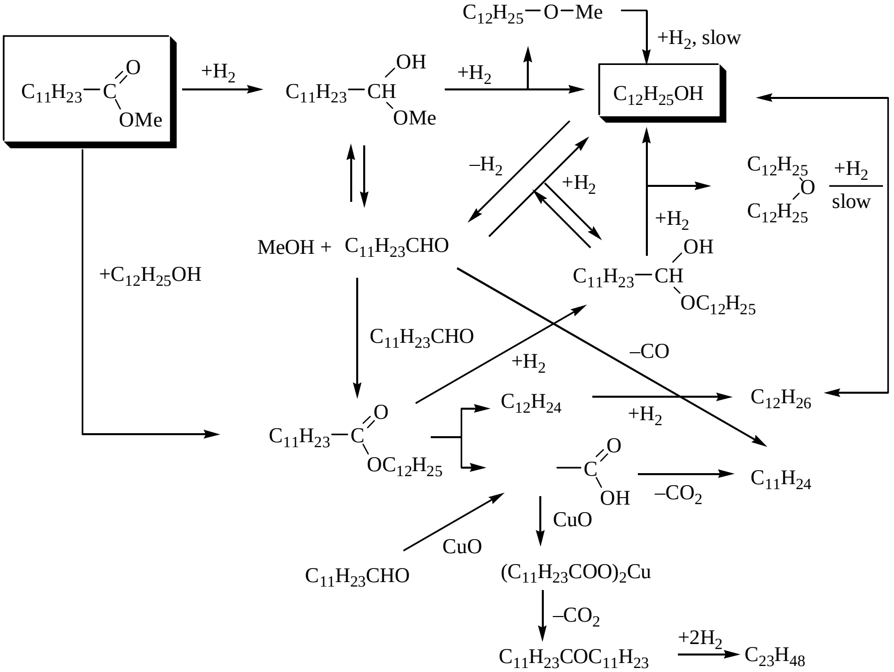
H_2. The equilibrium concentrations of esters may become higher with increasing temperatures. Usually for the hydrogen pressures above 21 MPa and temperatures below 260°C, the concentration of esters at equilibrium is very small and practically not important. As the most favorable conditions for the reaction at 250°C, Adkins recommends an initial hydrogen pressure of 24 MPa, the maximum pressure of 41 MPa at the temperature of reaction, and 21 MPa or higher at completion.[32] Typical hydrogenations of esters of mono- and dicarboxylic acids are given in eqs. 10.7[35] and 10.8,[36] respectively.

$$\underset{34\text{ g (0.2 mol)}}{C_7H_{15}CO_2Et} \xrightarrow[250°C,\ 20–30\text{ MPa } H_2,\ 2\text{ h}]{5\text{ g Cu–Ba–Cr oxide}} \underset{93.6\%}{C_7H_{15}CH_2OH} \quad (10.7)$$

$$\underset{252\text{ g (1.25 mol)}}{EtO_2C(CH_2)_4CO_2Et} \xrightarrow[255°C,\ 13.8–20.7\text{ MPa } H_2*,\ 6–12\text{ h}]{20\text{ g Cu–Cr or Cu–Ba–Cr oxide}} \underset{85–90\%}{HO(CH_2)_6OH} \quad (10.8)$$

* At room temperature.

The hydrogenation of fatty acids or fatty esters is of industrial importance for the production of fatty alcohols. Usually, the hydrogenation is performed in slurry-phase or fixed-bed reactors over copper–chromium oxide catalyst at elevated temperature and pressure.[37] Rieke et al. investigated the hydrogenation of methyl dodecanoate over copper–chromium oxide at 280°C and 13.8 MPa H_2, in order to study the side reactions that occur during hydrogenation.[37] On the basis of the potential reaction routes described by Rieke et al., the pathways leading to C_{12} alcohol and various byproducts are summarized in Scheme 10.2, with exclusion of the formation and reactions of acetals. It has been found that both catalytic activity and selectivity correlated well with the crystallinity of the copper–chromium ox-



Scheme 10.2 Potential reaction pathways leading to the alcohol and byproducts in the hydrogenation of methyl dodecanoate over copper–chromium oxide (based on the reaction routes described by Rieke et al., Ref. 37, p 335).

ide. Thus, the catalyst prepared by calcination at 399°C showed higher catalytic activity and selectivity than those obtained at 460 and 538°C, with formation of far decreased amounts of byproducts.[37]

Malonic esters, β-ketonic esters, and β-hydroxy esters, which are all hydrogenated to give 1,3-glycols, may undergo hydrogenolysis when hydrogenated at 250°C. Thus, diethyl malonate gave only ethyl propionate and its hydrogenation product 1-propanol, instead of the corresponding glycol, when hydrogenated at 250°C. Similarly, hydrogenation of ethyl β-hydroxybutyrate at 250°C yields 1- and 2-butanols (eq. 10.9).[35] In addition, the α-alkyl-substituted esters, which are expected to give 1,3-glycols on hydrogenation, may be accompanied by cleavage of the carbon–carbon linkage. Thus, while the hydrogenation of unsubstituted acetoacetic ester gave no product resulting from the C–C bond cleavage, ethyl 2-ethylacetoacetate was hydrogenated to give about 50% of 1-butanol, together with 2-ethyl-1-butanol. The C–C bond was cleaved almost quantitatively with the acetoacetic esters carrying an α substituent such as benzyl and hexahydrobenzyl. Similarly, hydrogenation of diethyl ethylmalonate was accompanied by formation of 18% of 1-butanol along with 72% of 2-methylbutanol (eq. 10.10).[38]

$$\underset{39.6\ \text{g (0.3 mol)}}{CH_3CHOHCH_2CO_2Et} \xrightarrow[250°\text{C, 20–30 MPa } H_2\text{, 5 h}]{6\ \text{g Cu–Ba–Cr oxide}} \underbrace{CH_3CH_2CH_2CH_2OH + CH_3CHOHCH_2CH_3}_{55.5\%} \tag{10.9}$$

$$\underset{43\ \text{g (0.23 mol)}}{CH_3CH_2CH(CO_2Et)_2} \xrightarrow[250°\text{C, 17.5 MPa } H_2\text{, 8 h}]{15\ \text{g Cu–Ba–Cr oxide}} \begin{array}{l} CH_3CH_2CH_2CH_2OH\ (18\%) \\ CH_3CH_2CH(CH_3)CH_2OH\ (72\%) \end{array} \tag{10.10}$$

The hydrogenolysis of glycols may be depressed largely if the hydrogenations are carried out at lower temperatures with a high catalyst:ester ratio.[39,40] Mozingo and Folkers hydrogenated β-oxygenated esters at temperatures between 150 and 180°C with use of relatively large amounts of copper–chromium oxide.[39] In contrast to the reactions at temperatures in excess of 220°C, the hydrogenation at the lower temperatures were most successful in methanol. Hydrogenations under these conditions of ethyl β-hydroxybutyrate or ethyl acetoacetate gave 1,3-butanediol in 30% yield. Ethyl β-ethoxypropionate gave a higher yield of the corresponding ethoxy alcohol (eq. 10.11).

$$\underset{146\ \text{g (1.0 mol)}}{EtOCH_2CH_2CO_2Et} \xrightarrow[\substack{100\ \text{ml MeOH} \\ 168\text{–}172°\text{C, 29–44 MPa } H_2\text{, 23 h}}]{30\ \text{g Cu–Ba–Cr oxide}} \underset{81.2\ \text{g (78\%)}}{EtOCH_2CH_2CH_2OH} \tag{10.11}$$

Under similar conditions, ethyl benzylmalonate, ethyl *s*-butylmalonate, and ethyl ethylmalonate were converted into the corresponding 1,3-glycols in 26, 24, and 49% yields, respectively. Adkins and Billica obtained 1,3-glycols in almost quantitative yields by hydrogenation of malonates, and β-oxo and β-hydroxy esters at temperatures 75–100°C below those required in usual hydrogenation, with use of a weight of catalyst as great or even greater than the weight of ester.[40] Examples are shown in eqs. 10.12 and 10.13 with ethyl acetoacetate and diethyl ethylmalonate, respectively.

$$\underset{10\ \text{g (0.077 mol)}}{CH_3COCH_2CO_2Et} \xrightarrow[\substack{75\ \text{ml EtOH} \\ 150°\text{C, 34.5 MPa } H_2\text{, 8.5 h}}]{15\ \text{g Cu–Cr oxide}} \underset{80\%\ \text{(isolated yield)}}{CH_3CHOHCH_2CH_2OH} \tag{10.12}$$

$$\underset{10\ \text{g (0.053 mol)}}{EtCH(CO_2Et)_2} \xrightarrow[\substack{75\ \text{ml EtOH} \\ 150°\text{C, 34.5 MPa } H_2\text{, 6.5 h}}]{15\ \text{g Cu–Cr oxide}} \underset{80\%\ \text{(isolated yield)}}{EtCH(CH_2OH)_2} \tag{10.13}$$

α-Hydroxy esters are hydrogenated under milder conditions than many other esters. Thus, aliphatic as well as aromatic α-hydroxy esters such as ethyl lactate (eq. 10.14) and ethyl mandelate (eq. 10.15) were hydrogenated to the corresponding 1,2-glycols rapidly at 125°C in the presence of large amounts of catalyst.[40] Ethyl benzilate was especially easily hydrogenated to the corresponding 1,2-glycols at 125°C with the use of only 1:8 catalyst:ester ratio (eq. 10.16).[41] Since 1,2-glycols are less susceptible to hydrogenolysis than 1,3-glycols and even 1,4-glycols, good yields of 1,2-glycols can

be obtained even in hydrogenations at 200–250°C, as seen in an example shown in eq. 10.17.[35]

$$\underset{10\text{ g }(0.085\text{ mol})}{CH_3CHOHCO_2Et} \xrightarrow[\substack{75\text{ ml EtOH} \\ 125°C,\ 34.5\text{ MPa } H_2,\ 0.2\text{ h}}]{15\text{ g Cu–Cr oxide}} \underset{80\%\text{ (isolated yield)}}{CH_3CHOHCH_2OH} \quad (10.14)$$

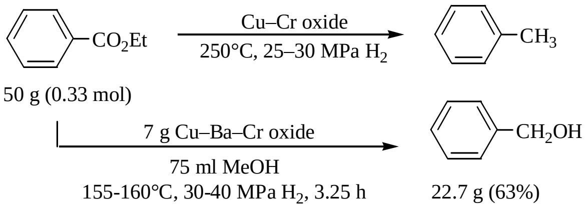
$$\underset{10\text{ g }(0.056\text{ mol})}{PhCHOHCO_2Et} \xrightarrow[\substack{75\text{ ml EtOH} \\ 125°C,\ 34.5\text{ MPa } H_2,\ 0.2\text{ h}}]{15\text{ g Cu–Cr oxide}} \underset{80\%\text{ (isolated yield)}}{PhCHOHCH_2OH} \quad (10.15)$$

$$\underset{40\text{ g }(0.156\text{ mol})}{Ph_2COHCO_2Et} \xrightarrow[125°C,\ 13.8\text{ MPa } H_2,\ 1\text{ h}]{5\text{ g Cu–Cr oxide}} \underset{77\%}{Ph_2COHCH_2OH} \quad (10.16)$$

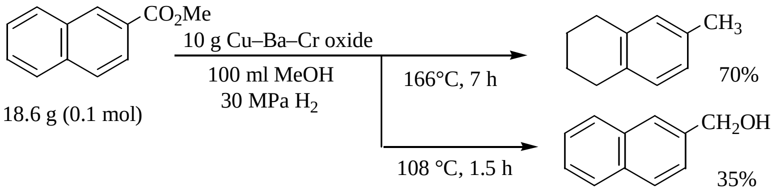
$$\underset{30\text{ g }(0.25\text{ mol})}{CH_3CHOHCO_2Et} \xrightarrow[250°C,\ 27.6\text{ MPa } H_2,\ 3.5\text{ h}]{5\text{ g Cu–Cr oxide}} \underset{91\%}{CH_3CHOHCH_2OH} \quad (10.17)$$

The hydrogenation of dimethyl cyclohexane-1,4-dicarboxylate to 1,4-cyclohexanedimethanol has been interested in an indusrial process for obtaining a useful diol component for polyesters, polyurethanes, and polycarbonates. The dimethyl dicarboxylate, usually prepared by the hydrogenation of dimethyl terephthalate over supported palladium catalysts, is hydrogenated over copper–chromium oxide in liquid phase or vapor phase.[42] Compared with the liquid-phase operation, the use of vapor-phase conditions has the advantage that generally operating pressures can be lowered. The 1,4-dimethanol rich in *trans* isomer (typically *trans/cis* ratio 2.0–3.84) was thus obtained in hydrogenation of a *cis*-rich diester (*trans/cis* ratio < 1, e.g., 0.5–0.6) with essentially complete conversion over granular copper–chromium oxide at 150–350°C and a feed pressure in the range of 1.03–13.8 MPa.[42a]

Benzoic and naphthoic esters are labile to hydrogenolysis to give hydrocarbons in hydrogenation at high temperature owing to the ready hydrogenolysis of resulting benzyl-type alcohols. However, these aromatic esters may undergo hydrogenation at temperatures much lower than those required for aliphatic esters, and it may be possible to obtain the corresponding alcohols in good yields, using methanol as the solvent. Examples are shown in eqs. 10.18[43] and 10.19[44] for ethyl benzoate and methyl 2-naphthoate, respectively.

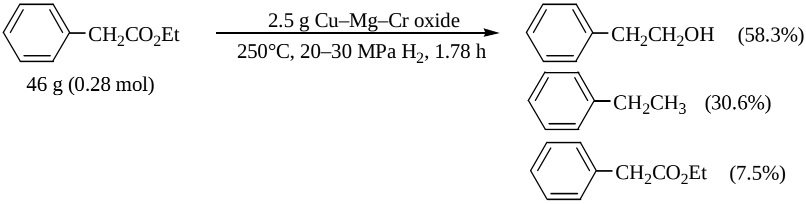


(10.18)



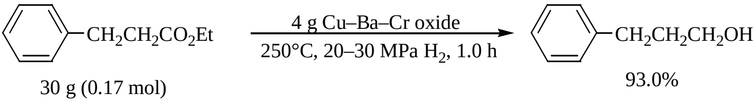
(10.19)

The tendency toward hydrogenolysis to give hydrocarbons is greatly reduced with phenylacetic esters where a homobenzyl-type alcohol is produced. If the hydrogenation was stopped before the absorption of hydrogen was complete, a 39.7% yield of 2-phenethyl alcohol was obtained over Cu–Ba–Cr oxide even at 250°C. The yield was further increased to 58.3% over Cu–Mg–Cr oxide (eq. 10.20), and the yields from the cyclohexyl ester was 58.7% over Cu–Ba–Cr oxide and 63.3% over Cu–Ca–Cr oxide. In contrast, over a catalyst containing no alkaline-earth metal oxide, the predominant product from the ethyl ester became ethylbenzene (88.7%), and 2-phenethyl alcohol was obtained in only 4.5% yield.



(10.20)

Further, in the case of ethyl 3-phenylpropionate with two CH_2 groups between the phenyl and the ester groups, the yield of the corresponding alcohol became almost quantitative over Cu–Ba–Cr oxide at 250°C (eq. 10.21).[35]



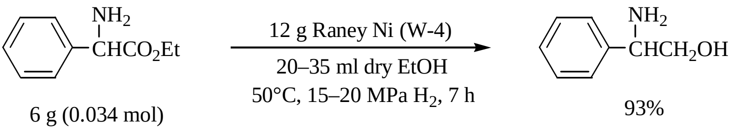
(10.21)

α-Amino esters are readily hydrogenated to amino alcohols over copper–chromium oxide catalyst in alcohols at 175°C or higher. Under these conditions alkylation of the amino group may take place. For example, the hydrogenation of methyl leucinate in ethanol at 175°C gave *N,N*-diethylleucinol in high yield (eq. 10.22).[45]

$$\underset{8\text{ g }(0.061\text{ mol})}{(CH_3)_2CHCH_2\overset{\overset{\displaystyle NH_2}{|}}{C}HCO_2Me} \xrightarrow[\substack{EtOH \\ 175°C,\ 20.7\text{ MPa }H_2,\ 7\text{ h}}]{10\text{ g Cu–Cr oxide}} \underset{83\%}{(CH_3)_2CHCH_2\overset{\overset{\displaystyle NEt_2}{|}}{C}HCH_2OH} \qquad (10.22)$$

α-Amino and α-hydroxy esters may be hydrogenated even at room temperature over an active Raney Ni such as W-4, W-5, and W-6. The reactions proceed rapidly at 50–100°C with use of a high catalyst:ester ratio (eqs. 10.23[46] and 10.24[40]). The addition

of a small amount of triethylamine decreased the time required for hydrogenation from 5.5 to 2 h in a hydrogenation of ethyl lactate.[47] The low-temperature hydrogenation of α-amino and α-hydroxy esters in the presence of triethylamine may also be advantageous in avoiding racemization of optically active esters and alcohols.[48]



(10.23)

$$CH_3CHOHCO_2Et \xrightarrow[\substack{25\text{–}75\text{ ml dry EtOH} \\ 100°C,\ 34.5\text{ MPa } H_2,\ 1.5\text{ h}}]{15\text{ g Raney Ni (W-6)}} CH_3CHOHCH_2OH \quad (10.24)$$

10 g (0.085 mol) → 80%

10.2.2 Hydrogenation of Unsaturated Esters to Unsaturated Alcohols

The hydrogenation of an unsaturated ester to an unsaturated alcohol may be possible over zinc–chromium oxide as catalyst, although the catalyst is known to be much less active for the usual ester hydrogenations than copper–chromium oxide. Ethyl or butyl (eq. 10.25) oleates were hydrogenated to octadecenol in yields of over 60% with a zinc–chromium oxide at 280–300°C and 20 MPa H_2.[16] The butyl ester was much preferred to the ethyl ester, since it was difficult to separate the ethyl ester from the alcohol product because of their similar boiling points.

$$C_{17}H_{33}CO_2Bu \xrightarrow[\substack{300°C,\ 20\text{ MPa } H_2,\ 11\text{ h} \\ 1.86\text{ mol } H_2}]{50\text{ g Zn–Cr oxide}} C_{17}H_{33}CH_2OH \quad (10.25)$$

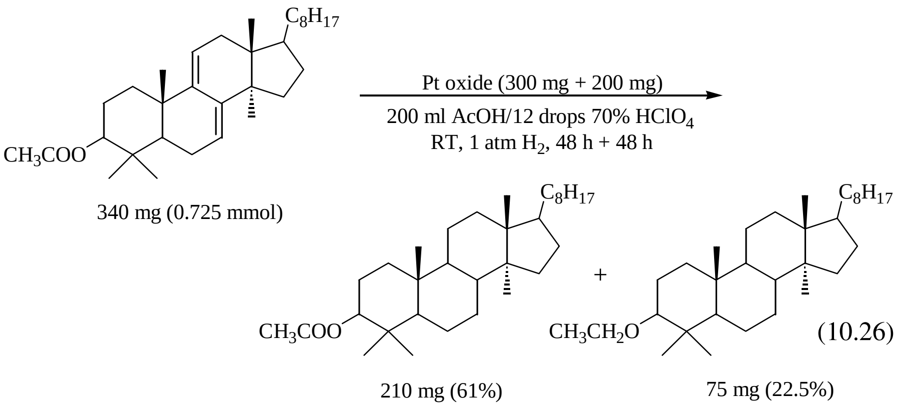
86 g (0.26 mol) → 65%*

* Contaminated with 13% of saturated alcohol.

An unsaturated alcohol $C_{21}H_{41}CH_2OH$ was also obtained in similar yield from butyl erucate (butyl 13-dococenoate). However, in the case of butyl 10-undecenoate, $CH_2{=}CH(CH_2)_8CO_2Bu$, the yield was only 37%. Subsequently, various catalyst systems have been described in the literature for the production of unsaturated alcohols from unsaturated acids and esters. Most of them are zinc oxide–based catalysts.[49] Narasimhan et al. reported a mixed-metal boride system ruthenium-tin boride to be effective for this purpose.[17] In the hydrogenation of methyl oleate over various Ru:Sn ratios of catalysts supported on γ-Al_2O_3, the optimum yield of oleyl alcohol and the selectivity for oleyl alcohol was obtained at an atomic ratio of Ru:Sn of 1:2. Thus, the hydrogenation of methyl oleate over a 1:2 Ru:Sn boride on Al_2O_3 at 270°C and 92.8 kPa H_2 (ester/H_2 = 1.23) for 6.5 h (80.8% conversion) gave a mixture of 60.4% of oleyl alcohol and 12.5% of stearyl alcohol, together with 10.0% of other products (methyl stearate and mostly low-molecular-weight ester and hydrocarbons). Ruthenium boride catalyst containing no Sn was highly active but nonselective for oleyl alcohol formation, and the products observed were all hydrocarbon fragments formed by hydrogenolytic cleavage of the C–C bonds of the ester.

10.2.3 Hydrogenation of Esters to Ethers

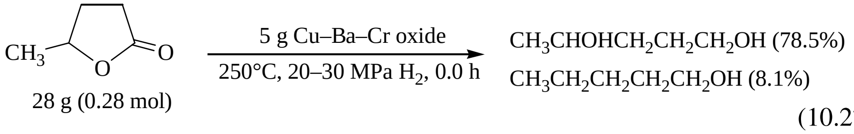
The carbonyl group in esters (and also in lactones and acid anhydrides) may be hydrogenated to methylene to give ethers, in particular, in strongly acidic medium over platinum oxide. Chanley and Mezzetti obtained a mixture of 3β-acetoxy- and 3β-ethoxy-5α-lanostanes by hydrogenation of 3β-acetoxy-5α-lanost-8-ene and 3β-acetoxy-5α-lanosta-7:8, 9:11-diene (eq. 10.26) in acetic acid containing perchloric acid with use of rather large amounts of platinum oxide.[1] Under similar conditions some δ-lactones derived from decalins and cholestanes have been hydrogenated to the corresponding ethers in much higher yields[50] (see the following section).



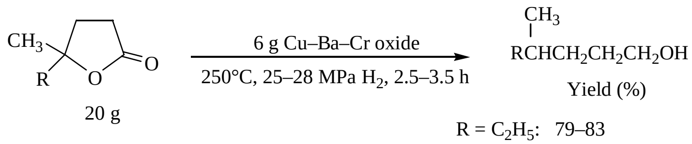
(10.26)

10.2.4 Lactones

Hydrogenation of lactones over copper–chromium oxide usually leads to the corresponding glycols. However, the formation of glycols is accompanied by the formation of small amounts of an alcohol that may result from the hydrogenolysis to give an acid. An example is shown in eq. 10.27 for the hydrogenation of γ-valerolactone.[35] Cason et al. obtained high yields (79–88%) of 4-alkyl-1-alkanols by hydrogenation of the tertiary lactones, γ-alkyl-γ-valerolactones, over copper–chromium oxide at 250°C and 25–28 MPa H_2 (eq. 10.28).[51]



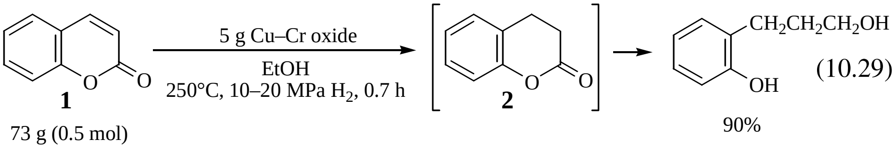
(10.27)



(10.28)

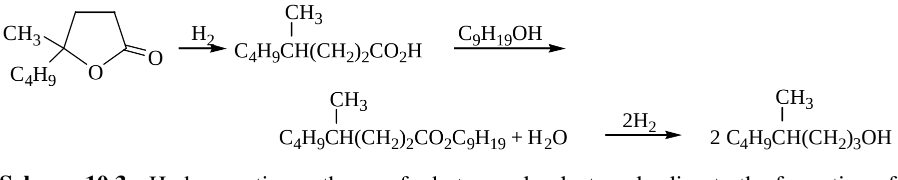
R = C_2H_5: 79–83
n-C_4H_9: 77–81
n-C_5H_{11}: 84
n-C_6H_{13}: 82–88

Detailed studies with γ-butyl-γ-valerolactone indicated that hydrogenation at lower temperatures increased the formation of the corresponding 1,4-glycol. The 1,4-glycol was hardly attacked at 200°C and converted to the monoalcohol much more slowly than did the lactone at 250°C. The corresponding tetrahydrofuran derivative, which was formed in only very small amounts, was hydrogenolyzed exceedingly slowly. In a hydrogenation of the lactone at 250°C over a poor grade of catalyst, the major product obtained was the ester, 4-methyloctyl 4-methyloctanoate, which was found to hydrogenate more rapidly than the lactone. From these findings it seemed reasonable that the rapid monoalcohol formation from the lactone until about 80% completion took place through the ester as intermediate (see Scheme 10.3). It was also suggested that the formation of the acid might occur either by direct hydrogenolysis or by hydrogenation of the unsaturated acid in equilibrium with the lactone.[51] The hydrogenation of lactones over nickel catalysts often leads to the formation of ethers. As an example, the hydrogenation of γ-butyrolactone and γ-valerolactone over Raney Ni at 200°C under a high pressure gave 9% of tetrahydrofuran and 17% of 2-methyltetrahydrofuran, respectively.[52] De Benneville and Connor studied the hydrogenation of coumarin (**1**) and related compounds over copper–chromium oxide and Raney Ni as catalysts.[53] Over copper–chromium oxide coumarin was converted in high yields into 3-(*o*-hydroxyphenyl)-1-propanol at 250°C via dihydrocoumarin (**2**) (eq. 10.29).

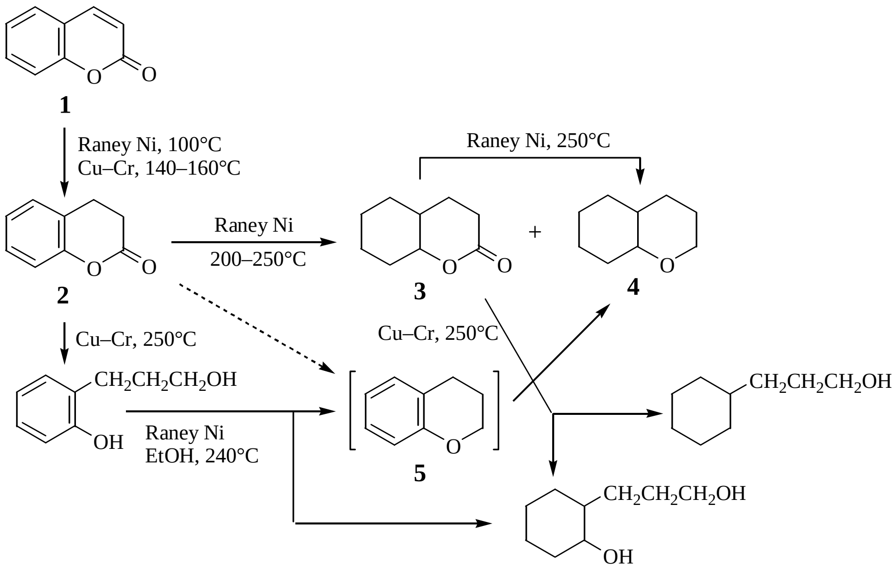


(10.29)

Over Raney Ni at 200–250°C, however, the main reactions of the dihydrocoumarin formed were saturation of the benzenoid ring to give octahydrocoumarin (**3**) and its conversion to the cyclic ether, hexahydrochroman (**4**), although polymeric products were also formed in 6–27% yields. The hydrogenation pathways and the products of coumarin and related compounds over copper–chromium oxide and Raney Ni are summarized in Scheme 10.4. For the formation of the cyclic ether **4** over Raney Ni,

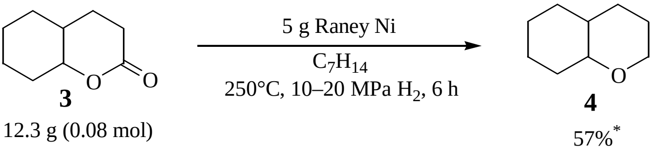


Scheme 10.3 Hydrogenation pathway of γ-buty-γ-valerolactone leading to the formation of 4-methyl-1-octanol.



Scheme 10.4 Hydrogenation pathways of coumarin over copper–chromium oxide and Raney Ni under 10–20 MPa H_2.

the pathway of **2** to chroman (**5**) (indicated by a dotted arrow) was suggested to be the least probable, since the structure aryl–O–CO– is not converted to aryl–O–CH_2– under these conditions.[54] The yields of **4** up to 35% were obtained from hydrogenation of **1** in a relatively long reaction period at 250°C, and a higher yield (57%) was obtained by hydrogenation of **3** under similar conditions (eq. 10.30).



(10.30)

* Recovery was low because of the high mechanical loss in a small-scale distillation.

Glattfeld and Schimpff hydrogenated the δ- and γ-lactones of aldonic acids over platinum oxide in aqueous solution.[24] In general, the δ-lactones were hydrogenated in good yield to the corresponding sugars. The γ-lactones usually gave lower yields of the sugars owing to further hydrogenation to the sugar alcohols. The rate of shaking was found to be an important factor for the reaction time. An example is shown for the hydrogenation of *d*-gluconic lactones (eq. 10.31).

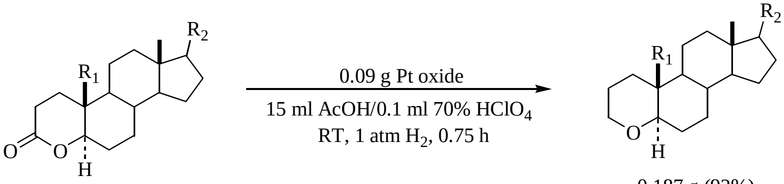
d-Gluconic lactone 3.562 g (0.02 mol) —[Pt oxide, 100 ml aq. soln. / RT, 0.2–0.3 MPa H_2]→ Sugar (%) + Acid (%) + Alcohol (%)

	Catalyst (g)	Agitation (cpm)*	Time (h)	Sugar (%)	Acid (%)	Alcohol (%)
δ-Lactone	0.2	120	33	55.1	17.8	27
δ-Lactone	2.0	350	0.58	80	19.0	0
γ-Lactone	2.0	350	1.0	46.8	12.4	41

* Cycles per minute.

(10.31)

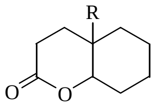
Edward and Ferland found that the hydrogenation of some δ-lactones over Adams platinum oxide in acetic acid or, better, in acetic acid with a small amount of perchloric acid, gave high yields of cyclic ethers, tetrahydropyrans.[50,55] Thus, the hydrogenation of 3-oxo-4-oxa-5α-cholestane (**6**: R_1 = Me, R_2 = C_8H_{17}) over platinum oxide in acetic acid afforded a 92% yield of 4-oxa-5α-cholestane. The hydrogenation was greatly accelerated from 9 to 0.75 h by addition of a proper amount of perchloric acid (e.g., 0.03 ml of 70% $HClO_4$ for 5 ml AcOH) (eq. 10.32). Similarly, 3-oxo-4-oxa-5β-cholestane (**6**: 5β-H, R_1 = Me, R_2 = C_8H_{17}), 17β-hydroxy-3-oxo-4-oxa-5α-estrane (**6**: R_1 = H, R_2 = OH), 2-oxo-1-oxadecalin (**7**: R = H) (*cis/trans* mixture), and 10-methyl-2-oxo-1-oxadecalin (**7**: R = Me) (*cis/trans* mixture) were hydrogenated to the cyclic ethers in yields of 80–90%. Under these conditions, there was no measurable uptake of hydrogen by several γ- and ε-lactones studied.



6: R_1 = Me, R_2 = C_8H_{17}
0.200 g (0.500 mmol)

0.187 g (92%)

(10.32)

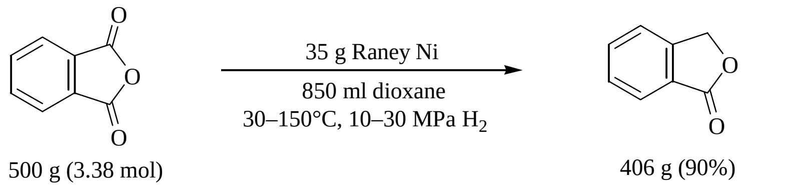


7

10.2.5 Acid Anhydrides

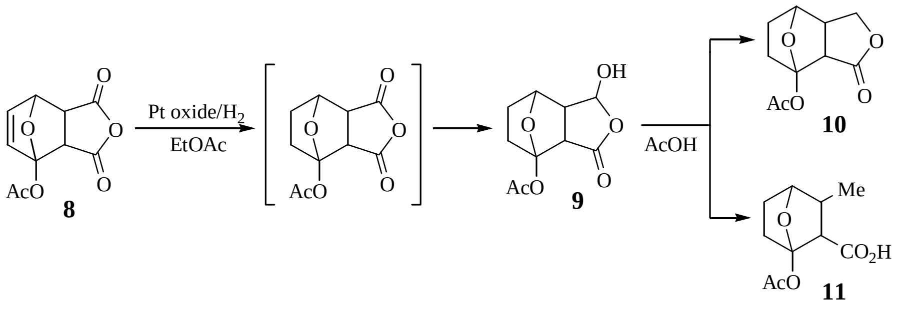
Hydrogenation of acid anhydrides such as succinic and phthalic anhydrides may give the corresponding lactones as well as more completely hydrogenated products. The hydrogenation of phthalic anhydride over Ni–kieselguhr at 150°C and 10–17 MPa H_2 gave a mixture of phthalide (34%), *o*-methylbenzoic acid (36%), and 2-methylcyclohexanecarboxylic acid (23%).[41] Phthalide was obtained in a high yield of 90% in the hydrogenation over Raney Ni at elevated temperature and pressure (eq. 10.33).[56] In one patent, phthalic anhydride was hydrogenated using a catalyst containing 98% CoO and 0.1% Na_2O at 200°C and 26 MPa H_2 to give 84% phthalide and 7.5% recov-

ered anhydride.[57] The hydrogenation of succinic anhydride over Cu–Ba–Cr oxide at 250°C and 20–30 MPa H_2 gave 29% of γ-butyrolactone, together with a considerable amount of very volatile material (butane?), tetrahydrofuran (?), butyric acid, succinic acid, and water.[58]

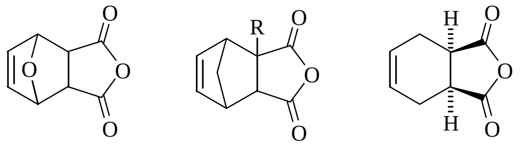


(10.33)

Acetic and propionic anhydrides are hydrogenolyzed to the corresponding aldehydes or alcohols and carboxylic acids when hydrogenated over rather large amounts of palladium and platinum catalysts at room temperature and 1 atm H_2. The aldehydes were the major products in the case of Pd–$BaSO_4$ and palladium black, while the alcohols were formed predominantly over platinum oxide, together with only small amounts of aldehydes.[59] McCrindle et al. studied the hydrogenation of substituted succinic anhydrides over platinum oxide.[60] Succinic anhydride gave a 4:1 mixture of butyrolactone and butyric acid in the hydrogenation in ethyl acetate at room temperature and 1 atm H_2. However, hydrogenation of substituted succinic anhydrides was found to give hydroxylactones and methyl acids as major products, depending on the compound, solvent, and time of reaction. Thus, the hydrogenation of the Diels–Alder adduct **8** over Adams platinum in ethyl acetate gave the hydroxylactone **9** in more than 90% yield, together with less than 2% of the lactone **10**. In acetic acid the lactone and the methyl acid **11** were obtained in comparable amounts (Scheme 10.5). The lactone was recovered unchanged under the same hydrogenation conditions, but the hydroxylactone gave a 2:1 mixture of the lactone and the methyl acid. These results indicated that the three products arose through the hydrogenation of the same anhydride carbonyl group. Hydrogenation of the structurally related anhydrides **12**–**14** gave similar results, although the proportion of the three possible products varied with the compounds.



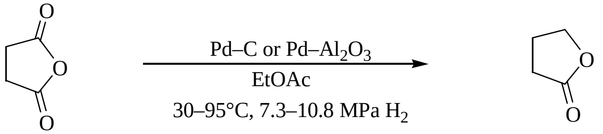
Scheme 10.5 Products of the hydrogenation of substituted succinic anhydride **8** over platinum oxide.



12 **13** **14**

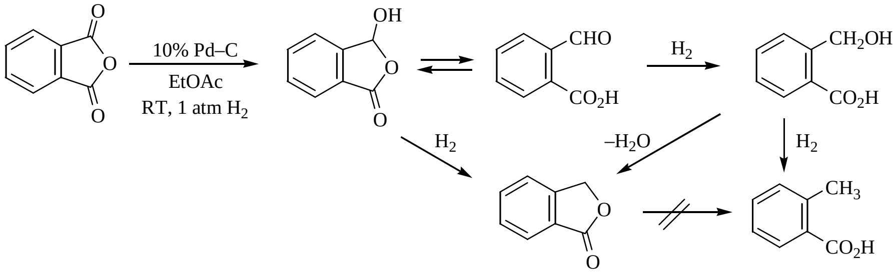
(R = H, Me)

When succinic anhydride was hydrogenated over palladium catalysts, γ-butyrolactone was produced in high yield in ethyl acetate at 30–95°C and 7.3–10.8 MPa H_2 (eq. 10.34).[61]



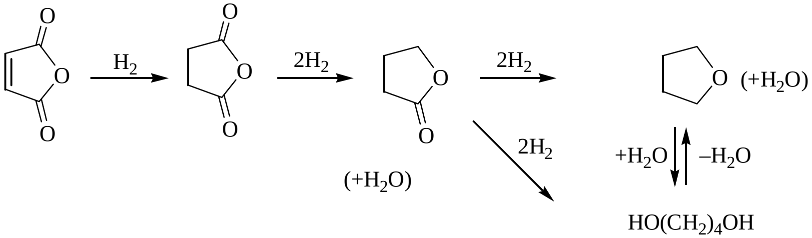
(10.34)

McAlees et al. studied the hydrogenation of various phthalic anhydrides over 10% Pd–C in ethyl acetate.[62] Hydrogenation of phthalic anhydride gave *o*-toluic acid in high yield. Either 3- or 4-substituted phthalic anhydrides may give phthalides and/or 2-(hydroxymethyl)benzoic acids in addition to *o*-toluic acids. In the case of 4-methoxyphthalic anhydride, the product mixture contained 35% of 2-(hydroxymethyl)-4-methoxybenzoic acid, together with 15% of 4-methoxy- and 50% of 5-methoxy-2-methylbenzoic acids, when the reaction was interrupted before hydrogen uptake was complete. Complete hydrogenation gave a mixture of equal amounts of 4- and 5-methoxy-2-methybenzoic acids. With 3- and 4-dimethylaminophthalic anhydrides, the corresponding 2-(hydroxymethyl)benzoic acids were present even when hydrogen uptake had almost ceased. Under the conditions of the hydrogenation, phthalide gave no *o*-toluic acid, whereas phthalaldehyde acid was rapidly hydrogenated to *o*-toluic acid. From these results, together with the findings on the intermediates with 3- and 4-substituted phthalic anhydrides, the hydrogenation routes, which involve *o*-hydroxymethylbenzoic acid as the intermediate leading to phthalide and *o*-toluic acid, have been suggested as illustrated in Scheme 10.6.



Scheme 10.6 Possible intermediates and reaction routes in the hydrogenation of phthalic anhydride over Pd–C.

Hydrogenation of maleic anhydride (or succinic anhydride) is of industrial importance for the manufacture of γ-butyrolactone, tetrahydrofuran, and 1,4-butanediol (Scheme 10.7).[63] Since the hydrogenation of maleic to succinic anhydride is highly exothermic (30 kcal or 125 kJ·mol^{-1}) and much faster than the subsequent hydrogenation, especially, the hydrogenation of γ-butyrolactone to tetrahydrofuran, in an industrial process maleic anhydride was diluted by the γ-butyrolactone formed as intermediate, so that the reaction conditions could become optimal for the latter hydrogenation. Further, since the hydrogenation is accompanied by the formation of water, which may produce acidic materials, a catalyst that is resistant to acid is required. By using a Ni–Re–kieselguhr catalyst[64] at 180–300°C and 4.9–14.7 MPa H_2, selectivity to tetrahydrofuran more than 90% could be obtained by means of a single-stage reactor. In this process, the product ratio of γ-butyrolactone to tetrahydrofuran could be controlled in a wide range. Some other catalyst systems that have been described in the literature for the hydrogenation of maleic anhydride and related compounds to γ-butyrolactone, tetrahydrofuran, or 1,4-butanediol are Ni–Cr–Mo oxide,[65] $NiMoO_2$, $CoMoO_3$,[66] and Ni–Co–Al_2O_3–kieselguhr,[67] and Cu–Cr[68] or supported Cu–Zn[69] in vapor phase process. The Cu–Zn–Al catalysts in which the Al content was in the range 17–24 (in atomic ratio) and Cu/Zn ratio between 0.5 and 1.0 was reported to give complete conversion of maleic anhydride and high yields (79–96%) of γ-butyrolactone in the vapor-phase hydrogenation of maleic anhydride/γ-butyrolacone mixture at 245–275°C, with better carbon balances, which might be attributed to lesser light hydrocarbon and tar formation.[70] Castiglioni et al. studied the effcts of the substitution with Cd, Zn, and Mg ions for Cu ions, which are contained in an excess in cubic spinel-type phases of copper–chromium oxide catalysts.[71] The substitution with Zn ion caused a slight decrease in the activity for γ-butyrolactone, but favored the hydrogenation of succinic anhydride to γ-butyrolactone. On the other hand, the partial substitution with Mg ions for Cu ions increased the productivity of γ-butyrolactone from maleic anhydride, inhibiting further hydrogenation and/or hydrogenolysis. In a fixed-bed process with a reduced CuO–ZnO–Al_2O_3-CrO_3 catalyst, maleic anhydride in ethanol (20% w/v) was hydrogenated at 235°C under 4.1 MPa H_2 containing 8% CO to give a product containing 94.1% THF, 4.2% butanol, and 1.1% propanol.[72] Maleic anhydride was also hydrogenated over 5% Ru–C in water at 240°C and 9.8 MPa H_2 to give a product con-



Scheme 10.7 Synthesis of γ-butyrolactone, tetrahydrofuran and 1,4-butanediol by hydrogenation of maleic anhydride.

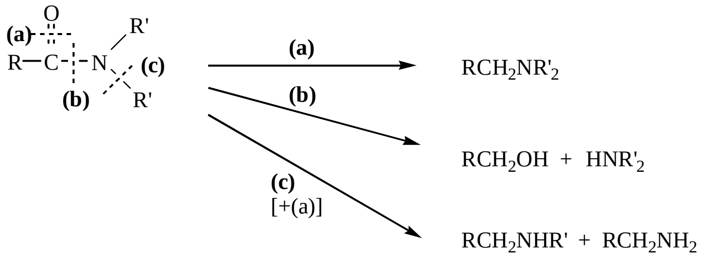
taining tetrahydrofuran 5.1, γ-butyrolactone 46.6, and 1,4-butanediol 24.1 mol% with 95.7 mol% conversion of maleic anhydride.[73] In a patent, γ-butyrolactone was transformed into tetrahydrofuran in 67.6 mol% yield in hydrogenation over 5% Ru–C in the presence of methanesulfonic acid in dimethoxyethane at 180°C and 4.9 MPa H_2.[74]

10.3 ACID AMIDES, LACTAMS, AND IMIDES

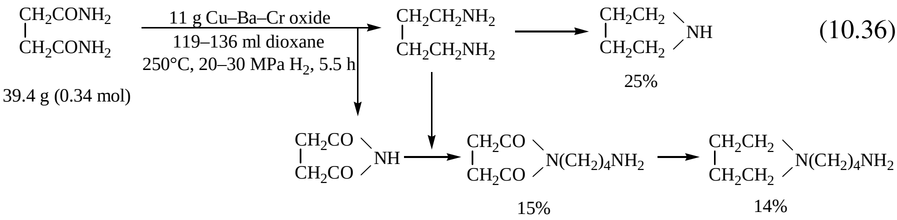
The hydrogenation of amides to amines, which involves the cleavage of the (**a**) linkage (see Scheme 10.8), usually requires rather drastic conditions, and the hydrogenolysis of other linkages indicated by (**b**) and (**c**) may occur concurrently, or in some cases predominantly.[75] An effective catalyst for the hydrogenation of amides to amines is copper–chromium oxide. The hydrogenation over this catalyst has been performed at 250–265°C and 20–30 MPa H_2, using 15% or more as much catalyst as amide.[76] In order to minimize the reaction of amides with the water formed, use of a solvent such as dioxane is necessary as a diluent of the water. In the case of *N*-unsubstituted amides, the yield of primary amine is reduced by the formation of secondary amine. By carrying out the hydrogenation rapidly using a high catalyst:amide ratio and stopping the reaction just before the hydrogenation is complete, the yield of primary amine may be improved. As a typical example for an unsubstituted amide, the hydrogenation of lauramide is given in eq. 10.35.

$$\underset{20\text{ g (0.10 mol)}}{C_{11}H_{23}CONH_2} \xrightarrow[\substack{35\text{–}40\text{ ml dioxane} \\ 250^\circ\text{C, 20–30 MPa } H_2\text{, 0.8 h}}]{\text{4 g Cu–Ba–Cr oxide}} \underset{48\%}{C_{12}H_{25}NH_2} + \underset{49\%}{(C_{12}H_{25})_2NH} \quad (10.35)$$

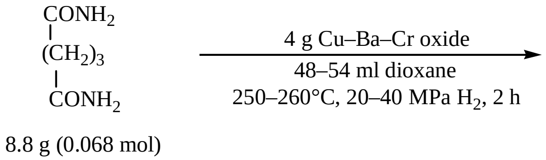
With succinamide, the major products were pyrrolidine and *N*-substituted pyrrolidine, which might be formed through the reaction paths shown in eq. 10.36.[76] Under similar conditions, the hydrogenation of glutaramide gave piperidine in high yield (eq. 10.37).[77]



Scheme 10.8 The cleavage of the linkages in the hydrogenation of acid amides.



(10.36)



(10.37)

Cleavage at the (**c**) linkage in Scheme 10.8 occurs almost exclusively in the case of *N,N*-disubstituted amides, as in an example shown with *N,N*-diethyllauramide (eq. 10.38).[76]

$$\underset{38\text{ g }(0.15\text{ mol})}{C_{11}H_{23}CONEt_2} \xrightarrow[\substack{53\text{–}60\text{ ml dioxane} \\ 250°\text{C, }20\text{–}30\text{ MPa }H_2\text{, }0.5\text{ h}}]{8\text{ g Cu–Ba–Cr oxide}} \underset{64\%}{C_{12}H_{25}NHEt} + \underset{30\%}{(C_{12}H_{25})_2NH} \qquad (10.38)$$

Cleavage at (**c**) took place to a considerable extent with an *N*-monosubstituted amide as well, together with a small extent of cleavage at the (**b**) linkage (eq. 10.39). The cleavage at (**b**) becomes more important with an *N*-phenyl-substituted amide as shown in eq. 10.40. It is noted that cleavage at (**b**) may lead to the products formed by cleavage at (**a**) through the reactions shown in Scheme 10.9.[78]

$$\underset{59\text{ g }(0.22\text{ mol})}{C_{11}H_{23}CONHC_5H_{11}} \xrightarrow[\substack{77\text{–}88\text{ ml dioxane} \\ 250°\text{C, }20\text{–}30\text{ MPa }H_2\text{, }0.01\text{ h}}]{10\text{ g Cu–Ba–Cr oxide}} \underset{15\%}{C_{12}H_{25}NH_2} + \underset{35\%}{C_{12}H_{25}NHC_5H_{11}} + \underset{42\%}{(C_{12}H_{25})_2NH} + \underset{8\%}{(C_5H_{11})_2NH} \qquad (10.39)$$

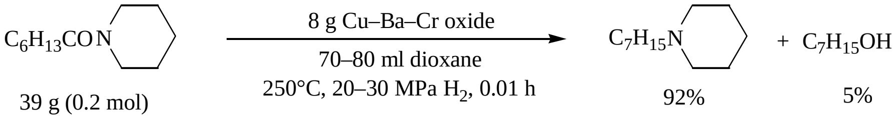
$$\underset{49\text{ g }(0.18\text{ mol})}{C_{11}H_{23}CONHPh} \xrightarrow[\substack{63\text{–}72\text{ ml dioxane} \\ 250°\text{C, }20\text{–}30\text{ MPa }H_2\text{, }3.2\text{ h}}]{10\text{ g Cu–Ba–Cr oxide}} \underset{14\%}{C_{12}H_{25}NH_2} + \underset{37\%}{C_{12}H_{25}NHPh} + \underset{2\%}{(C_{12}H_{25})_2NH} + \underset{29\%}{PhNH_2} + \underset{5\%}{Ph_2NH} \qquad (10.40)$$

Cleavage at (**b**) and (**c**) (see Scheme 10.8) is stabilized with *N*-acylpiperidines (eq. 10.41), while with *N*-benzoylpiperidine the products resulting from cleavage at (**b**) became predominant (eq. 10.42).[62]

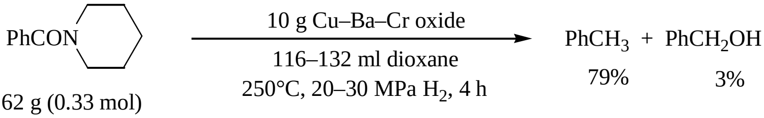
$$\mathrm{RCONHR' + 2H_2 \longrightarrow RCH_2OH + R'NH_2}$$

$$\mathrm{RCH_2OH + R'NH_2 \longrightarrow RCH_2NHR' + H_2O}$$

Scheme 10.9 The hydrogenation pathway of amides to amines involving hydrogenolysis of the carbonyl carbon–nitrogen bond.



(10.41)



(10.42)

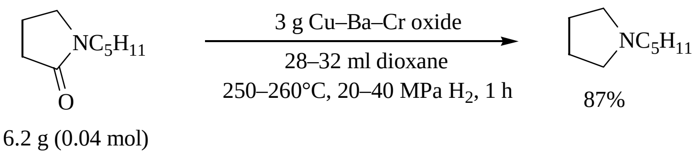
Amides are also hydrogenated to amines over rhenium catalyst at 185–245°C under high pressures of hydrogen. Acetamide,[79] *N*-phenylacetamide,[79] and *N*-ethyl-*N*-phenylacetamide[10] were hydrogenated to the corresponding amines in high yields over rhenium catalysts (eq. 10.43). It is noted that over rhenium catalysts the secondary amine formation with *N*-unsubstituted amide as well as cleavage at the (**b**) and (**c**) linkages with *N*-substituted amides take place not at all or only at a low level.

$$\underset{15\ \mathrm{g}\ (0.25\ \mathrm{mol})}{\mathrm{CH_3CONH_2}} \xrightarrow[\substack{25\ \mathrm{ml\ cyclohexane} \\ 200^\circ\mathrm{C},\ 20.5\ \mathrm{MPa\ H_2\ at\ RT},\ 18\ \mathrm{h}}]{0.2\ \mathrm{g\ ReO_3}} \underset{88\%}{\mathrm{CH_3CH_2NH_2}}$$

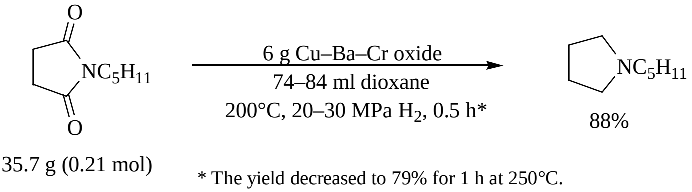
$$\underset{15\ \mathrm{g}\ (0.11\ \mathrm{mol})}{\mathrm{CH_3CONHPh}} \xrightarrow[\substack{25\ \mathrm{ml\ cyclohexane} \\ 185^\circ\mathrm{C},\ 20.5\ \mathrm{MPa\ H_2\ at\ RT},\ 31\ \mathrm{h}}]{0.2\ \mathrm{g\ ReO_3}} \underset{71\%}{\mathrm{CH_3CH_2NHPh}} + \underset{29\%}{\mathrm{H_2NPh}}$$

$$\underset{50\ \mathrm{g}\ (0.31\ \mathrm{mol})}{\mathrm{CH_3CON(Et)(Ph)}} \xrightarrow[\substack{\mathrm{EtOH} \\ 245^\circ\mathrm{C},\ 35.2\ \mathrm{MPa\ H_2},\ 22\ \mathrm{h}}]{1\ \mathrm{g\ Re_2O_7}} \underset{95\%}{\mathrm{Et_2NPh}} \qquad (10.43)$$

Cyclic amides or imides such as *N*-substituted 2-pyrrolidones and succinimides are converted in high yields to the corresponding pyrrolidines over Cu–Ba–Cr oxide (eqs. 10.44[77] and 10.45[76]). Similarly, *N*-substituted 2-piperidone was hydrogenated to the corresponding piperidine in high yield (eq. 10.46).[77] Under the same conditions, *N*-substituted phthalimides were hydrogenated to give hexahydrobenzopyrrolidines, as seen in eq. 10.47[76]:

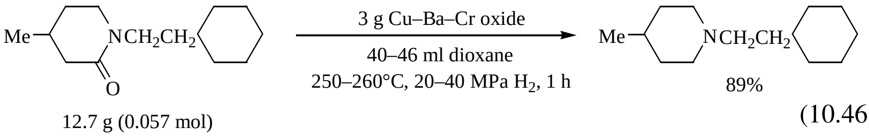


(10.44)

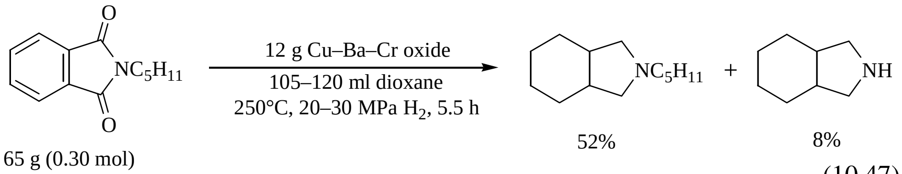


(10.45)

* The yield decreased to 79% for 1 h at 250°C.

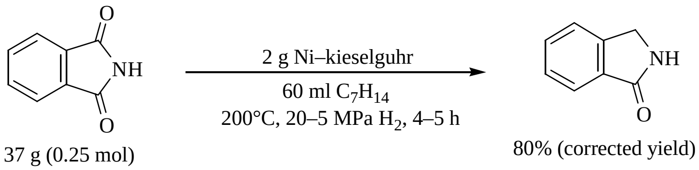


(10.46)

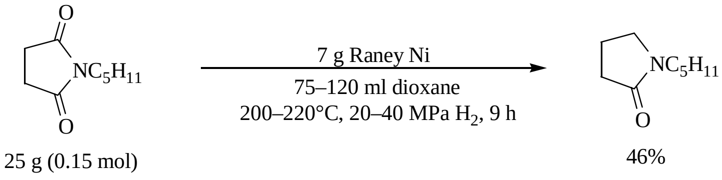


(10.47)

Over nickel catalysts, phthalimide (eq. 10.48),[80] and *N*-substituted succinimides and glutarimides are hydrogenated to give the lactams at 200–220°C.[77] Hydrogenations were rather slow at these temperatures, but use of dioxane for Raney Ni at temperatures above 220°C should be avoided.[81] The reaction with *N*-pentylsuccinimide (eq. 10.49) was incomplete even after two applications of catalyst. The low yield of the pyrrolidone probably resulted from the difficulty of separating the pyrrolidone from the imide.

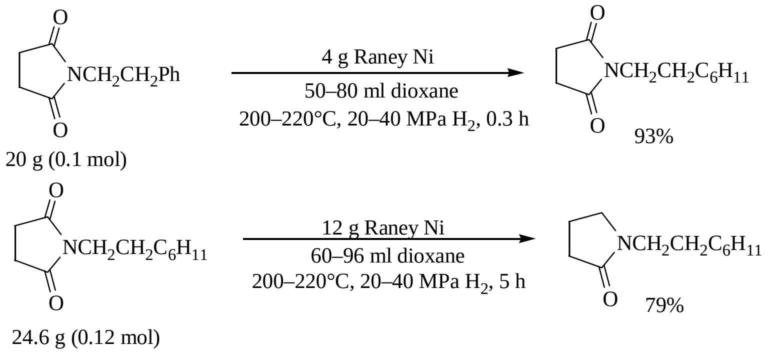


(10.48)



(10.49)

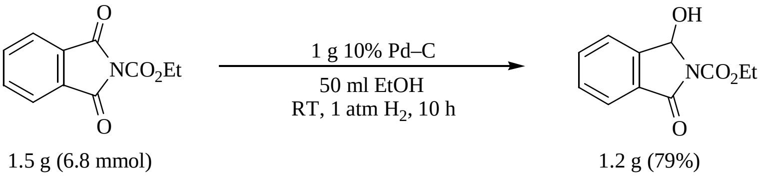
In cases of *N*-β-phenethylimides, the first reaction was saturation of the benzene ring, which occurred rapidly at 200°C. When the hydrogenation was interrupted after 20 min, *N*-(2-cyclohexylethyl)succinimide could be isolated in a yield of 93%, and it was hydrogenated to give the corresponding pyrrolidone in 79% yield (eq. 10.50).



(10.50)

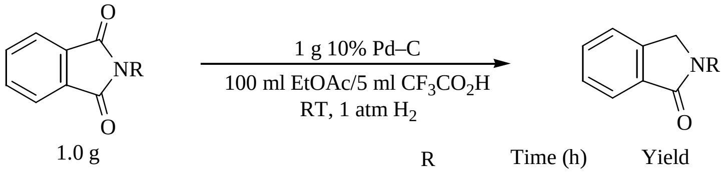
Similarly, hydrogenation of *N*-phenethyl-β-methylglutarimide gave the corresponding *N*-cyclohexylethylpiperidone in 74% yield. In one patent, 3,4,5,6-tetrahydrophthalimide was successfully hydrogenated to give octahydroisoindole in 65% yield over Raney Ni in cyclohexane at 250°C and 14.7 MPa H_2.[82]

McAlees and McCrindle found that phthalimides with electron-withdrawing substituents such as an acyl or alkoxycarbonyl on the imide nitrogen were hydrogenated to the corresponding 3-hydroxyisoindolin-1-ones over 10% Pd–C in ethyl acetate or ethanol (eq. 10.51).[83]



(10.51)

Phthalimide and *N*-methylphthalimide were not hydrogenated under these conditions. However, it has later been shown that the hydrogenation was markedly promoted in the presence of trifluoroacetic acid, and under these conditions phthalimide and *N*-alkylphtalimides could also be hydrogenated.[84] The products obtained were isoindolin-1-ones, which were presumed to be formed through the 3-hydroxy derivatives as intermediates (eq. 10.52). The relative rates for the *N*-substituted phthalimides (see eq. 10.52)—*N*-COMe > *N*-CO_2Et > NH > *N*-Me > *N*-$CHMe_2$ ~ *N*-CMe_3—were in the order to be expected if nucleophilic attack on a carbonyl carbon atom were involved.



(10.52)

R	Time (h)	Yield
COMe	2	0.78 g (84%)
CO_2Et	3	0.85 g (91%)
H	8	0.85 g (94%)
Me	12	0.95 g (100%)
$CHMe_2$	32	75% hydrogenation
CMe_3	43	85% hydrogenation

Phthalimide was also hydrogenated to give isoindolin-1-one with addition of a small amount of iron(II) sulfate, although more slowly than in the presence of trifluoroacetic acid. Hexahydrophthalimide and *N*-ethoxycarbonylsuccinimide resisted hydrogenation even in the presence of trifluoroacetic acid.

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CHAPTER 11

Hydrogenation of Aromatic Compounds

11.1 AROMATIC HYDROCARBONS

In contrast to olefinic compounds, aromatic hydrocarbons are seldom hydrogenated at room temperature over base metals and palladium catalysts. This difficulty for hydrogenation probably comes from the situation that the benzene nucleus is stabilized by 151 kJ (36 kcal)·mol^{-1} as a result of the resonance hybridization.[1] However, at elevated temperatures (and pressures) most aromatic hydrocarbons are hydrogenated without difficulty over nickel and cobalt catalysts.[2–5] Over ruthenium and, particularly, over rhodium and platinum, benzene and its derivatives may be hydrogenated at considerable rates even at room temperature.[6–8] The rate of hydrogenation of methyl-substituted benzenes generally decreases with increasing number of the methyl substituents (see Table 11.1). Among the isomers with the same number of methyl substituents, the symmetrically substituted isomer is hydrogenated faster than the unsymmetrically substituted ones. For example, with dimethylbenzenes the rate increases in the order 1,2- < 1,3- < 1,4-dimethyl. With trimethyl- and tetramethylbenzenes, 1,3,5 and 1,2,4,5 isomers, respectively, are hydrogenated most rapidly. From a series of studies on the hydrogenation of alkyl-substituted benzenes over Ni–Al_2O_3, Lozovoi and D'yakova concluded that neither the length nor the structure of aliphatic side chains excerted any practical influence on the rate of hydrogenation, although the rate was influenced by the number of the substituents present in the benzene nucleus.[9]

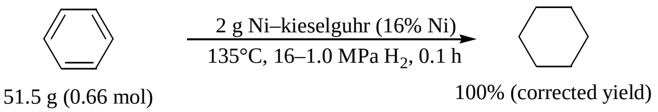
Orito and Imai have shown that the hydrogenation of benzene over nickel and cobalt catalysts is inhibited by alcoholic solvents and some ethers.[5] As seen from the results shown in Table 11.2, benzene is hydrogenated extremely slowly or not at all in primary alcohols but very rapidly without solvent or in hydrocarbons. Benzene is hydrogenated at a considerable rate at 110°C even over Urushibara Ni A, which is known to be a poor catalyst toward the hydrogenation of aromatic nucleus,[10] when used without solvent or in hydrocarbons after the water or alcohol on the catalyst has been carefully removed.

Adkins and Kramer hydrogenated benzene and alkylbenzenes to the corresponding cyclohexanes quantitatively over Ni–kieselguhr without solvent at 135–175°C and initial hydrogen pressures of 15.5–18 MPa.[11] Examples are shown in eqs. 11.1 and 11.2 for hydrogenations of benzene and toluene, respectively. Mesitylene was hydrogenated to 1,3,5-trimethylcyclohexane at 200°C (eq. 11.3).[12] Triphenylmethane was hydrogenated to tricyclohexylmethane in methylcyclohexane at 175°C. However, hydrogenation in ethanol or in the presence of water gave dicyclohexylphenylmethane

TABLE 11.1 Relative Rates of Hydrogenation of Methyl-Substituted Benzenes over Platinum and Nickel Catalysts

	Catalyst		
Benzene	Adams Pt[a]	Raney Ni[b]	Ni–Al_2O_3[c]
Benzene	100	100	100
Methyl-	62	77	50
1,2-Dimethyl-	32	16	24
1,3-Dimethyl-	49	21	23
1,4-Dimethyl-	65	26	31
1,2,3-Trimethyl-	14	—	—
1,2,4-Trimethyl-	29	—	—
1,3,5-Trimethyl-	58	—	10
1,2,3,4-Tetramethyl-	10	—	—
1,2,3,5-Tetramethyl-	11	—	—
1,2,4,5-Tetramethyl-	18	—	3.8
Pentamethyl-	3.5	—	0.5
Hexamethyl-	0.2	—	~0

[a]AcOH, 30°C, 0.4 MPa H_2; k (benzene) = 4.3×10^{-3} mol · min^{-1} · g cat^{-1} (Data of Smith, H. A.; Pennekamp, E. F. H. *J. Am. Chem. Soc.* **1945**, *67*, 279. Reprinted with permission from American Chemical Society.).
[b]170°C, 3.9 MPa H_2; k (benzene) = 4.9×10^{-2} mol · min^{-1} · g cat^{-1} (Wauquier, J.-P.; Jungers, J. C. *Bull. Soc. Chim. Belg.* **1957**, *66*, 1280. Reprinted with permission from Société Royale de Chimie, Belgium.).
[c]Over 65% Ni–Al_2O_3 at 20–230°C and H_2 pressure ≤20 MPa (Lozovoi, A. V.; D'yakova, M. K. *J. Gen. Chem.* (*USSR*) **1938**, *8*, 105; **1939**, *9*, 895; *CA* **1938**, *32*, 5287[4]; **1940**, *34*, 388[4]).



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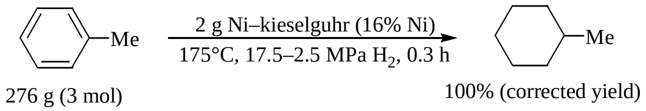

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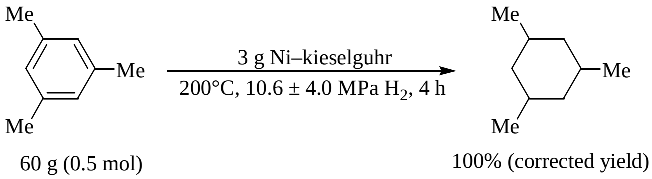


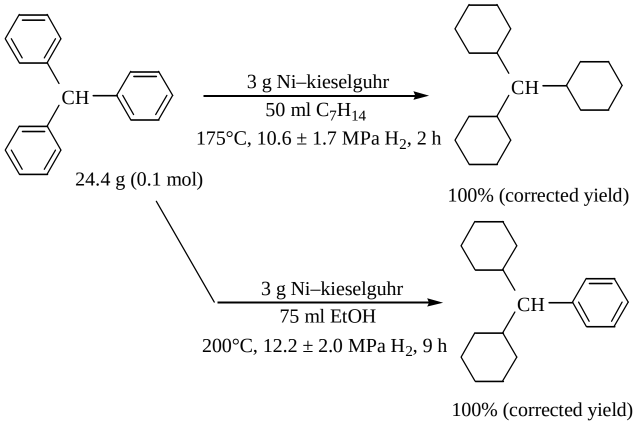
(11.3)

in even a longer reaction time at 200°C (eq. 11.4). Dicyclohexylphenylmethane in ethanol solution absorbed no hydrogen at 200°C and 10 MPa H_2.[12] According to the results by Adkins and co-workers, Ni–kieselguhr is usually superior to Raney Ni for the hydrogenation of aromatic compounds.[2] For example, 60 min was required for the hydrogenation of benzene to cyclohexane over 18 wt% of Raney Ni at 150°C, com-

TABLE 11.2 The Effect of Solvents on the Rate of Hydrogenation of Benzene over Nickel and Cobalt Catalysts[a,b]

	Catalyst				
Solvent	$Ni–Cr_2O_3–K$[c]	Raney Ni[d]	U-Ni–A[e]	$Co–Cr_2O_3–K$[f]	Raney Co[g]
None	112	460	326	46	178
Cyclohexane	110	449	188	103	154
Heptane	113	495	220	96	154
MeOH	3	0	—	0	—
EtOH	3	3	0	0	0
BuOH	4	—	—	—	—
Cyclohexanol	20	—	—	—	—
i-PrOH	29	62	0	—	—
s-BuOH	32	66	2	1	7
t-BuOH	34	—	—	—	—
i-Pr_2O	46	135	18	43	—
1,4-Dioxane	1	5	0	0	—

[a]Data of Orito, Y.; Imai, S. *Shokubai* **1962**, *4*, 5; *Tokyo Kogyo Shikensho Hokoku* **1963**, *58*, 119 [*CA* **1965**, *62*, 424]. Reprinted with permission from Catalysis Society of Japan.
[b]Benzene (60 ml without solvent or 20 ml with 40 ml solvent for the supported catalysts; 45 ml without solvent or 15 ml with 30 ml solvent for Raney and Urushibara catalysts) was hydrogenated at initial hydrogen pressure of 4 MPa. The rates (ml $H_2 \cdot min^{-1}$) were obtained at initial stages for unsupported catalysts or as average values at H_2 pressure drop from 4 to 3 MPa for Raney and Urushibara catalysts.
[c]1:0.1:1 $Ni–Cr_2O_3$–kieselguhr 1.0 g; 90°C.
[d]Prepared from 3.0 g of 50% Ni–Al alloy; 70°C.
[e]Urushibara Ni A (1.0 g Ni); 110°C.
[f]1:0.1:1 $Co–Cr_2O_3$–kieselguhr 1.0 g; 80°C.
[g]Prepared from 3.0 g of 45% Co–Al alloy; 70°C.



(11.4)

TABLE 11.3 Rates of Hydrogenation of Aromatic Hydrocarbons over Nickel and Cobalt Catalysts[a,b]

	Rate of Hydrogenation × 10^3 (mol · min^{-1} · g $metal^{-1}$)			
Catalyst	Benzene	Toluene	*o*-Xylene	Naphthalene[c]
Raney Ni[d]	8.3	3.3	2.2	23.3
Raney Co[e]	16.8	8.3	3.9	32.9
P-1 Ni boride[f]	6.3	2.7	2.2	7.9
P-1 Co boride[f]	14.8	6.5	1.9	21.2

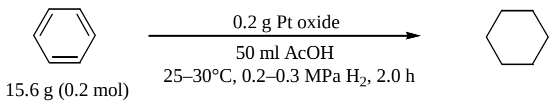
[a]Ohnuki, A.; Nishimura, S. Unpublished results; Ohnuki, A. Master's thesis, Tokyo Univ. Agrc. Technol. (1992).
[b]Benzene (113 mmol), toluene (95.7 mmol), *o*-xylene (83.0 mmol) or naphthalene (31.3 mmol) was hydrogenated over the catalyst containing 0.08 g of metal in 10 ml methylcyclohexane (cyclohexane for toluene) at 80°C and an initial hydrogen pressure of 7.8 MPa. The rates were obtained at the initial stages of hydrogenation.
[c]Hydrogenation to tetrahydronaphthalene.
[d]A $NiAl_3$ alloy was developed to 87.5–88.5% in the presence of bayerite at 40°C (Nishimura et al. *Appl. Catal.* **1991**, *76*, 19).
[e]A Co_2Al_9 alloy was developed to 83–86% in the presence of bayerite at 40°C (Nishimura et al. *Appl. Catal.* **1991**, *76*, 19).
[f]Prepared by reduction of nickel or cobalt acetate with $NaBH_4$ in water according to the procedure of Brown (Brown, C. A. *J. Org. Chem.* **1970**, *35*, 1900).

pared to only 10 min with 5 wt% of Ni–kieselguhr at 125°C. However, the results shown in Table 11.2 suggest that the activity of Raney Ni might have been partly poisoned by the water used for preparation of the Raney Ni or the alcohol used for washing, which might remain on the catalyst.

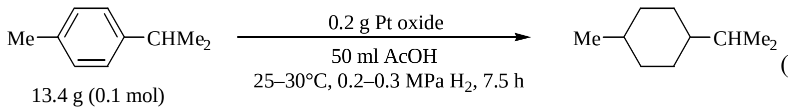
Cobalt catalysts are generally known to be less active than nickel catalysts for the hydrogenation of aromatic compounds (see, e.g., Table 11.2).[4,5] However, properly prepared reduced cobalt or Raney Co have been reported to be more active than the corresponding nickel catalysts in the hydrogenation of benzene[13–15] and naphthalene.[15]

P-1 Ni[16] and P-1 Co[17] boride catalysts have also proved to be good catalysts for the hydrogenation of aromatic hydrocarbons. Table 11.3 compares the activities of these nickel and cobalt catalysts in the hydrogenation of some aromatic hydrocarbons in hydrocarbon solvent at 80°C and the initial hydrogen pressure of 7.8 MPa.[18] It is noted that, as in the cases of Raney Ni and Raney Co, P-1 Co boride is generally more active than P-1 Ni boride, except for *o*-xylene.

Over platinum metals such as platinum, rhodium, and ruthenium, aromatic compounds can be hydrogenated even at room temperature and a low hydrogen pressure. Adams and Marshall hydrogenated various aromatic hydrocarbons with use of the Adams platinum oxide in acetic acid at 25–30°C and 0.2–0.3 MPa H_2, although often a long reaction time was required.[6] Examples are shown in eqs. 11.5 and 11.6.



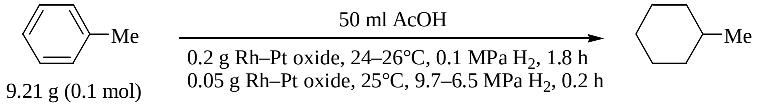
(11.5)



(11.6)

Benzene cannot be hydrogenated over Adams platinum in a neutral solvent even at an elevated temperature and pressure. However, Keenan et al. have shown that benzene is hydrogenated over Adams platinum without addition of acetic acid, if the alkaline substances contaminated into the oxide during the fusion procedure had been removed by prereducing the oxide in methanol or acetic acid and washing the resulting metal.[19] The situation with Adams platinum oxide that the alkaline materials prevent the hydrogenation of benzene is also true for the rhodium or rhodium–platinum oxide prepared by the Adams procedure[20,21] and for the Pichler's ruthenium dioxide.[22] Similar to the platinum oxide, acetic acid is an excellent solvent for the hydrogenation of aromatic compounds with the rhodium or rhodium–platinum oxides, whereas it may inhibit the hydrogenation over ruthenium catalysts under mild conditions.

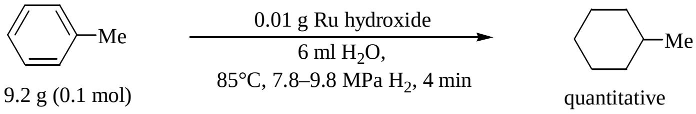
Rhodium catalysts have been shown to be highly active in the hydrogenation of aromatic compounds. Gilman and Cohn found that 5 ml of benzene was hydrogenated 4 times as rapidly with 1 g of 5% Rh–Al_2O_3 as with 1 g of 5% Pt-Al_2O_3 in acetic acid under ordinary conditions.[7] Nishimura found that the rhodium–platinum oxides (Rh:Pt = 90–70:10–30), prepared by a modified Adams procedure, exhibited higher activities than did either pure rhodium oxide or platinum oxide in the hydrogenation of aromatic compounds in acetic acid under ordinary conditions. For example, toluene (0.01 mol) was hydrogenated with the initial hydrogen uptake rates of 103–110 ml · min^{-1} over 0.05 g of the rhodium–platinum oxides (4.2–4.5 × 10^{-2} · mol · min^{-1} · g $metal^{-1}$) in 20 ml of acetic acid at 30°C and atmospheric pressure, compared to 88 and 19 ml · min^{-1} over rhodium oxide and platinum oxide, respectively. As with Adams platinum oxide,[23] or even more effectively, the rhodium–platinum oxides can catalyze many hydrogenations much more rapidly under high pressures of hydrogen than at atmospheric pressure, as seen from the following example:[24]



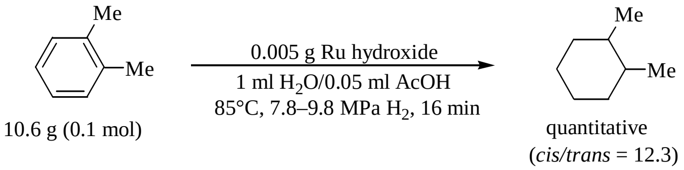
(11.7)

Benzene is also hydrogenated readily over 5% Ru–C without solvent or in the presence of water at 25°C and 6.9 MPa H_2. Toluene, ethylbenzene, and xylenes were hydrogenated at 100°C and 6.9 MPa H_2. The presence of water was often found to greatly promote ruthenium-catalyzed hydrogenations.[25] Ruthenium and rhodium catalysts, which contain much lesser amounts of alkaline substances than the rhodium oxide of Adams' type as well as Pichler's ruthenium dioxide, have been prepared from rhodium and ruthenium hydroxides, which were carefully precipitated from their chlorides with use of a slight excess of aqueous sodium hydroxide, followed by thorough washings with water until the pH of the filtrate became 7.8.[26] Toluene (eq. 11.8) and *o*-xylene (eq. 11.9) were hydrogenated rapidly with the ruthenium hydroxide thus

prepared at 85°C and 7.8–9.8 MPa H_2 in the presence of water or the water added by a slight amount of acetic acid.



(11.8)



(11.9)

Aromatic hydrocarbons may also be hydrogenated over transition metal oxides and sulfides at higher temperatures and pressures. Lozovoi and Senyavin found that the rates of hydrogenation of alkyl-substituted benzenes over MoO_2 at 380 or 420°C under high hydrogen pressure were almost unaffected by the introduction of 1–5 methyl groups, in contrast to the previous results obtained with Ni–Al_2O_3 as catalyst.[27] Further, in the hydrogenation of alkylbenzenes over WS_2 at 420°C and 20 MPa H_2, the relative rates (given in parentheses) were benzene (1), toluene (2.3), *m*-xylene (3.3), mesitylene (4.3), pentamethylbenzene (6.3), and hexamethylbenzene (1.5).[28] Thus, benzene was hydrogenated most slowly and pentamethylbenzene most rapidly over WS_2. The benzene which contained sulfur compounds was transformed into cyclohexane in 97.5% yield over 28% WS_2-4% NiS–Al_2O_3 at about 345°C and 30 MPa H_2.[29] Kalechits et al. compared the activities and selectivities of various sulfided catalysts in the hydrogenation, isomerization, and dissociation of benzene at 420°C and 20 MPa H_2. The order in hydrogenation activity was WS_2–NiS–Al_2O_3 ≥ Pt–F–Al_2O_3 > WS_2 > MoS_2 > MoS_2–C > Co–Mo–Al_2O_3 > WS_2–terrana. The order in isomerization activity was WS_2–terrana > WS_2 > MoS_2 > Pt–F–Al_2O_3 > WS_2–NiS–Al_2O_3 > Co–Mo–Al_2O_3 > MoS_2–C. Thus, MoS_2–C, which showed a high activity and a negligible isomerizing activity, could be employed for the selective hydrogenation of benzene to cyclohexane at 380–420°C and 24 MPa H_2; 93–95% pure cyclohexane was obtained.[30] Benzene was also hydrogenated to cyclohexane rapidly and quantitatively over rhenium oxide catalysts at 177–240°C and ~20 MPa H_2.[31,32]

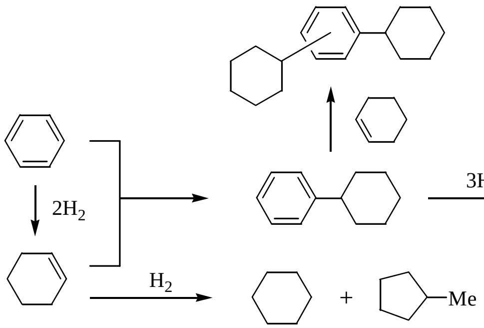
11.1.1 Hydrogenation of Benzene to Cyclohexene

In 1975 Johnson and Nowack reported that benzene was hydrogenated to cyclohexene in 20.3% yield at 58% conversion over a cobalt ion (0.05%) modified 0.5% Ru–$Ca(OH)_2$ in the presence of water at 180°C and 6.8 MPa H_2.[33] The yield of cyclohexene was definitely higher than those ever reported for the cyclohexene intermediate in the hydrogenation of benzene.[34–36] Similar nickel- and iron-ion-modified 0.5% Ru–$Ca(OH)_2$ or nickel-modified 0.5% Ru–Al_2O_3 also gave good selectivities to cyclohexene although in somewhat lower yields than over the cobalt-modified catalyst. It appears that the presence of water and small amounts of transition metal

ions, together with a rather high reaction temperature, have contributed to the high selectivity to cyclohexene. Since then, a number of investigations on the selective hydrogenation of benzene to cyclohexene have appeared in the literature focusing on application to an industrial process for the production of cyclohexene, which may be an intermediate, such as for ε-caprolactam. In one patent, 29–30% yields of cyclohexene were obtained in the hydrogenation of benzene over a 5% Ru–0.5% Cu–Al_2O_3 modified with $CoSO_4$ in the presence of water at 170°C and 3.9 MPa H_2.[37] Niwa et al. obtained a 31.4% yield of cyclohexene at 83.3% conversion of benzene over a 2% Ru–0.2% Cu–SiO_2 in the presence of water at 180°C and 7 MPa H_2 without any additive.[38] The Ru–Cu–SiO_2 catalyst was prepared by mixing a $RuCl_3$ solution in ethylene glycol with tetraethyl orthosilicate at 65°C, followed by hydrolysis with addition of water.[39] In a patent, 40.5% yield of cyclohexene at 75.8% conversion of benzene was obtained over 2% Ru–2% Co–0.2% Cu–$BaSO_4$ in the presence of water with addition of $CoSO_4 \cdot 7H_2O$ at 180°C and 3.9 MPa H_2.[40] In another patent, 42.1% yield of cyclohexene at 71.1% conversion was obtained over a ruthenium black in the presence of water with addition of $ZnSO_4 \cdot 7H_2O$ and 1-naphthol at 150°C and 4.9 MPa H_2.[41] In a similar catalyst and additive system, 49.2% yield of cyclohexene was obtained with 64% conversion of benzene with use of an autoclave whose inner surface and stirring rod were coated with a molybdenum-containing nickel alloy.[42] A composite mixture of lanthanum oxide and nitrates deposited on high-surface-area SiO_2 was claimed to be effective as a support for the ruthenium catalyst in the hydrogenation of benzene to cyclohexene.[43] The hydrogenation of benzene over this catalyst in an aqueous cobalt sulfate at 150°C and 4.5 MPa H_2 gave a maximum yield of 39.1% cyclohexene at 84.1% conversion, compared to only 6.9% yield with a Ru–SiO_2 catalyst without the lanthanum compounds in the support. Nagahara et al. studied the effects of the addition of small amounts of alcohols using 1% Ru–$La(OH)_3$,[44] 1% Ru–γ-Al_2O_3, and ruthenium black as catalysts.[45] In general, the addition of alcohols decreased the rate of hydrogenation of benzene and increased the selectivity to cyclohexene. When benzyl alcohol(0.337 g) was added to the reaction mixture (80 ml benzene/320 ml H_2O) with ruthenium black (0.2 g) in the presence of 0.431 g $ZnSO_4 \cdot 7H_2O$ and 45.7 g Na_2SO_4 at 150°C and 5.1 MPa H_2, 70% selectivity to cyclohexene was attained at 30% conversion. It is noted that the effect of the addition of benzyl alcohol was different with the catalysts. Ru–$La(OH)_3$ was deactivated by benzyl alcohol much more significantly than ruthenium black, and the addition of *n*-BuOH was the most favorable for the Ru–$La(OH)_3$-catalyzed hydrogenation (68.5% selectivity at 31.5% conversion).

The high yields of cyclohexene in the presence of water may be related to the observation that the hydrogenation proceeds in the aqueous phase, where benzene is much more soluble than cyclohexene.[46–49] Therefore, it is important that the catalyst be hydrophilic.[50]

Hydrogenation of benzene over acidic catalysts or in the presence of acid results in the formation of the products resulting from alkylation by the intermediate cyclohexene such as cyclohexylbenzene, together with cyclohexane, as shown in Scheme 11.1. Slaugh and Leonard obtained cyclohexylbenzene in high selectivity in the hy-



Scheme 11.1 Formation of cyclohexylbenzene and related coupled products in the hydrogenation of benzene over acidic catalysts.

drogenation of benzene over a variety of acidic supported transition metal catalysts.[51] For example, cyclohexylbenzene was obtained in a selectivity of 79.2% at 14% conversion in hydrogenation of benzene at 200°C and 5.5 MPa H_2 over a nickel catalyst prepared by calcinating 75% SiO_2–25% Al_2O_3 impregnated with NiF_2 at 500–550°C (5.2% Ni and 2.4% F), together with the formation of 7.8% cyclohexane, 0.5% methylcyclopentane, 4.3% of cyclohexylcyclohexane, and 8.3% of C_{18} products.[51] Dannels and Shepard hydrogenated benzene mixed with hydrogen fluoride over a platinum or rhodium catalyst at room temperature and 0.1–0.5 MPa H_2 and obtained cyclohexylbenzene amounting to 25% by weight of the hydrogenation products.[52]

Yasuhara and Nishino studied the hydrogenation of benzene over supported platinum group metals in the presence of various strong acids.[53] Cyclohexanol and its derivatives ($C_6H_{11}X$: X = OAc, Cl, Br) were produced by the hydrogenation of benzene with the corresponding acid additives. For example, 2 ml of benzene was hydrogenated in 5 ml of 35% HCl over 0.2 g of 5% Pd–SiO_2 at 100°C and 1 MPa H_2 for 20 h to give chlorocyclohexane in 8.4% yield (64.2% selectivity) at 13.1% conversion of benzene.

11.1.2 Hydrogenation of Polyphenyl Compounds to Cyclohexylphenyl Derivatives

Hydrogenation of aromatic compounds containing more than one benzene nucleus often results in the formation of the intermediate cyclohexylphenyl derivatives in high yields. Smith et al. obtained essentially pure cyclohexylphenyl intermediates in the half-hydrogenation of diphenylmethane and 1,1-diphenylethane, and, similarly, a minimum of 90% phenylcyclohexylacetic acid from diphenylacetic acid over Adams platinum oxide at 30°C and initial hydrogen pressures of 0.44 MPa.[54] Under the same conditions, biphenyl and benzilic acid (diphenylglycolic acid) gave the corresponding cyclohexylphenyl derivatives in 60 and 65% yields, respectively. The yields of the intermediates thus obtained were much higher than those expected from the rate ratios for individual hydrogenations of the parent diphenyl compounds and the corresponding intermediate cyclohexylphenyl derivatives (0.88 for biphenyl, 0.946 for diphenyl-

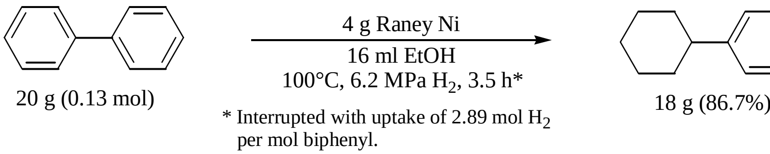
TABLE 11.4 Selective Hydrogenation of Biphenyl and Diphenylmethane over Platinum Metals[a]

					Composition of Reaction Mixture (mol%)		
Substrate	Catalyst	T (°C)	Solvent	H_2 Uptake (mol)	Biphenyl or Diphenylmethane	Cyclohexylbenzene or Cyclohexylphenylmethane	Bicyclohexyl or Dicyclohexylmethane
Biphenyl[b]	5% Pd–C	100	AcOH	~3	10	87	3
			C_6H_{12}	~3	3	97	0
	5% Pt–C	100	AcOH	Poisoned	—	—	—
			C_6H_{12}	~3	12	56	32
	5% Rh–C	100	AcOH	~3	15	58	27
			C_6H_{12}	~3	21	43	36
	5% Ru–C[c]	100	AcOH	~3	36	31	33
			C_6H_{12}	~3	35	34	31
	5% Rh–Al_2O_3	100	AcOH	~3	29	61	10
	15% Ir–C	100	C_6H_{12}	~3	40	37	23
Diphenylmethane[d]	5% Pd–C	119	AcOH	2.46	26	66	8
	5% Pt–C	102	AcOH	3.06	18	62	20
	5% Rh–C	87	AcOH	3.75	18	39	43
	5% Rh–C[e]	35	None	1.74	54	34	12
	PtO_2	32	AcOH	2.55	34	47	19

[a]Data of Rylander, P. N.; Steele, D. R. *Engelhard Ind. Tech. Bull.* **1965**, *5*, 113. Reprinted with permission from Engelhard Corporation.
[b]Biphenyl (5–10 g) was hydrogenated over 0.6 g of 5% metal–C or 0.3 g of 15% Ir–C in 25 ml solvent under 6.9 MPa H_2.
[c]Plus 10 ml of water in the ruthenium hydrogenation.
[d]Unless otherwise noted, 10 ml of diphenylmethane was hydrogenated over 0.6 g of 5% metal–C or 0.2 g of Pt oxide under 6.9 MPa H_2.
[e]25 ml substrate and 0.3 g catalyst.

methane, 1.30 for 1,1-diphenylethane, 0.953 for diphenylacetic acid, and 0.896 for diphenylglycolic acid). Rylander and Steele studied the selectivity of the six supported platinum metal catalysts for formation of the intermediate cyclohexylphenyl derivatives in the hydrogenation of biphenyl and diphenylmethane (Table 11.4).[55] The highest selectivity was obtained in the hydrogenation of biphenyl over palladium catalyst in cyclohexane (100°C and 6.9 MPa H_2), where cyclohexylbenzene was formed in 97% yield. Diphenylmethane was hydrogenated with less selectivity than biphenyl. The highest yield of cyclohexylphenylmethane obtained was 66% over 5% Pd–C (acetic acid solvent, 119°C, 6.9 MPa H_2). The selectivity obtained with platinum oxide was lower than that reported by Smith et al., who obtained essentially pure cyclohexylphenylmethane by distillation, as described above.

The hydrogenation of biphenyl over Raney Ni in ethanol appears to proceed selectively to give cyclohexylbenzene in high yield (see eq. 11.4). Goodman obtained cyclohexylbenzene in high yield by hydrogenation of biphenyl over Raney Ni in ethanol at 100°C and 6.2 MPa H_2 and interrupting the reaction at the end of the first, rapid pressure drop, although further hydrogenation appeared to proceed only very slowly and rapid hydrogenation to bicyclohexyl occurred only at 200°C (eq. 11.10).[56] Adkins and Billica hydrogenated biphenyl quantitatively to cyclohexylbenzene with the use of a rather large amount of Raney Ni (W-6) (2 g for 5.2 g of biphenyl) in ethanol at 25–30°C and 0.10–0.31 MPa H_2.[57]



(11.10)

Hall and Cawley hydrogenated biphenyl over pelleted molybdenum sulfide at 350°C and 20–30 MPa H_2, and obtained cyclohexylbenzene, benzene and cyclohexane, and dicyclohexyl, along with their isomerides.[58]

11.1.3 Stereochemistry of Hydrogenation

The studies of Skita[59] and von Auwers[60] revealed that, when the aromatic hydrocarbons with two or more nuclear substituents were hydrogenated, the products obtained over platinum in acidic media under mild conditions were isomeric and not identical in their physical properties with those obtained in vapor-phase hydrogenation over Sabatier's nickel catalyst. With isomeric xylenes, for example, the products obtained over platinum were assigned to be the *cis* isomers and those with the nickel catalyst at a high temperature to be the *trans*, although it was later shown by Pitzer in 1947 that the more stable isomer of 1,3-dimethylcyclohexane is the *cis*[61] and, therefore, the isomer from hydrogenation of *m*-xylene over the nickel catalyst should be the *cis*.

Linstead et al. explained the selective formation of *cis*-*syn*-*cis*-perhydrophnanthrene in the hydrogenation of phenathrene over Adams platinum in acetic acid on the basis that the hydrogen atoms were added to one side of the molecule from the catalyst

surface during a single period of adsorption insofar as the hydrogenation of one aromatic ring was concerned.[62] However, Siegel et al. have shown that considerable amounts of the *trans* isomers were formed in the hydrogenation of isomeric xylenes over Adams platinum in acetic acid. The amounts of the *trans* isomers formed increased in the order: 8% with *o*-xylene < 23% with *m*-xylene < 27% with *p*-xylene.[63] Siegel et al. have also shown that the stereochemistry of the hydrogenation of isomeric xylenes is closely related to those of the corresponding tetrahydro intermediates that may desorb from the catalyst surface during hydrogenation. In general, the stereoselectivity of the hydrogenation of aromatic compounds depends greatly on the nature of catalyst metal. In the hydrogenation of *o*-xylene over the platinum metals, the highest selectivity to the *cis* isomer was obtained with iridium (99.2%) and osmium (97.9%), and the lowest with palladium (57.7%). As pointed out by Siegel et al., the varying stereoselectivities with the catalyst metals in the hydrogenation of *o*-xylene are in parallel with those of the same catalyst metals for 1,6- and, in particular, 1,2-dimethylcyclohexene, as seen from the results shown in Table 11.5.[64] For *m*- and *p*-xylenes, the highest stereoselectivities to the *cis* isomer were also obtained over iridium and osmium (10.3 and 9.6% for *m*-xylene; 11.1 and 18.3% for *p*-xylene in isopropyl alcohol at 25°C), although the stereoselectivities were much lower than those with *o*-xylene.[65]

Rylander et al. studied the effect of carriers and water on the stereochemistry of hydrogenation of *o*-, *m*-, and *p*-xylenes over rhodium and ruthenium catalysts at room temperature and an initial hydrogen pressure of 0.44 MPa.[66] As seen from the results shown in Table 11.6, carbon-supported catalysts give less *trans* isomers than do the other supported catalysts. With a few exceptions, rhodium catalysts tend to produce the *trans* isomers more than do ruthenium catalysts. It is noted that the presence of water greatly reduced the proportion of *trans* isomer in the hydrogenations of *o*- and *m*-xylenes with Ru–C and of *p*-xylene with Rh–C.

TABLE 11.5 Stereoselectivities of the Platinum Metals for Formation of the *Cis* Isomer in the Hydrogenation of *o*-Xylene, and 1,2- and 1,6-Dimethylcyclohexene[a,b]

	cis-1,2-Dimethylcyclohexane (%)		
Catalyst	*o*-Xylene	1,2-Dimethylcyclohexene	1,6-Dimethylcyclohexene
Ir	99.2	99.2	89.0
Os	97.9	98.7	87.0
Rh	95.8	87.6	78.5
Ru	94.6	93.5	86.9
Pt	89.6	76.4	72.6
Pd[c]	57.7	25.9	25.6

[a]Data of Nishimura, S. *Yuki Gosei Kagaku Kyokaishi* **1972**, *30*, 36. Reprinted with permission from Society of Synthetic Organic Chemistry, Japan.
[b]Unless otherwise noted, the substrate (0.10–0.15 ml) was hydrogenated over unsupported metals (7.5–40 mg) in 4–5 ml of *t*-BuOH at 26°C and atmospheric hydrogen pressure.
[c]Hydrogenated at 50°C with use of 40–80 mg of Pd.

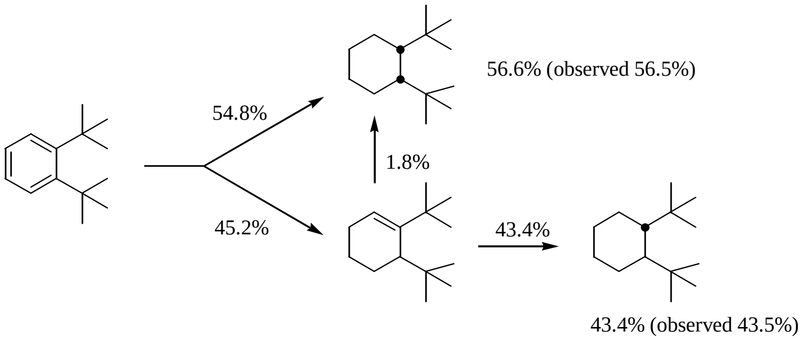
TABLE 11.6 Effects of Carriers and Water on the Stereochemistry of Hydrogenation of *o*-, *m*-, and *p*-Xylenes with Rhodium and Ruthenium Catalysts[a,b]

	% *Trans* Isomer in Dimethylcyclohexane from Hydrogenation of		
Catalyst	*o*-Xylene	*m*-Xylene	*p*-Xylene
5% Rh–C	6.5	15.6	22.7
5% Rh–C[c]	5.4	17.5	9.4
5% Rh–kieselguhr	7.1	19.7	31.9
5% Rh–$SrCO_3$	8.0	23.8	25.0
5% Rh–$BaCO_3$	15.8	30.3	30.3
5% Rh–$BaSO_4$	14.2	18.2	34.5
5% Rh–Al_2O_3	8.0	27.8	29.5
5% Ru–C	3.0	9.3	23.8
5% Ru–C[c]	< 0.5	< 0.5	23.8
5% Ru–kieselguhr	6.0	—	27.0
5% Ru–$SrCO_3$	4.3	11.8	31.8
5% Ru–$BaCO_3$	3.6	15.7	27.6
5% Ru–$BaSO_4$	5.2	14.4	—
5% Ru–Al_2O_3	9.7	14.7	29.4

[a]Data of Rylander, P. N.; Kilroy, M.; Coven, V. *Engelhard Ind. Tech. Bull.* **1965**, *6*, 11. Reprinted with permission from Engelhard Corporation.
[b]Xylenes were hydrogenated at room temperature and 0.44 MPa initial hydrogen pressure.
[c]Hydrogenated in the presence of an equal volume of water with xylene.

Van de Graaf et al. studied the hydrogenation of 1,2-di-*t*-butylbenzene over rhodium and platinum catalysts at 25°C and atmospheric hydrogen pressure.[67] Hydrogenation over 5% Rh–C proceeds much faster than in the corresponding dialkylbenzenes with methyl, ethyl, or isopropyl substituents. The high hydrogenation rate of 1,2-di-*t*-butylbenzene has been explained by a partial elimination of steric strain on hydrogenation.[68] The *trans* isomer of the saturated product, 1,2-di-*t*-butylcyclohexane, was found to arise exclusively through the intermediate 1,6-di-*t*-butylcyclohexene, the hydrogenation of which gave the *trans* isomer in large excess (96.5% in acetic acid). 1,6-Di-*t*-butylcyclohexene was formed in 30.1 and 45.2% yields at the maximum in ethanol and in acetic acid, respectively, together with *cis*-1,2-di-*t*-butylcyclohexane, and was hydrogenated only after almost all of 1,2-di-*t*-butylbenzene had been consumed. On the basis of these results, the hydrogenation pathways of 1,2-di-*t*-butylbenzene over 5% Rh–C can be formulated as in Scheme 11.2.

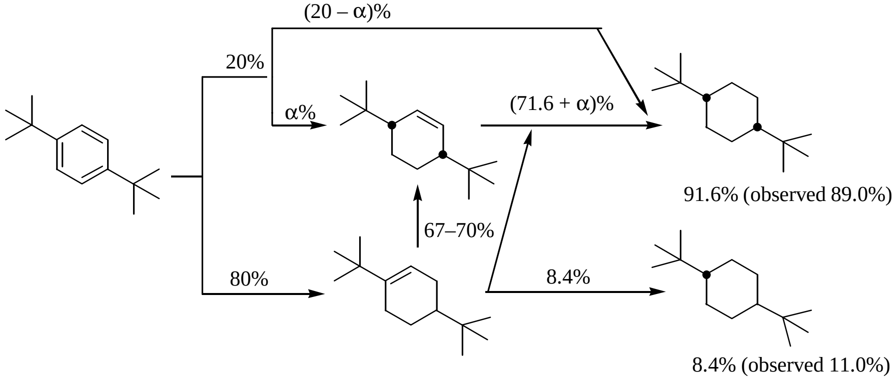
Siegel et al. observed that, at low hydrogen pressures (0.03–0.2 MPa), about 80% of the initial products from 1,4-di-*t*-butylbenzene formed over 5% Rh–Al_2O_3 in cyclohexane was 1,4-di-*t*-butylcyclohexene; the remainder was *cis*-1,4-di-*t*-butylcyclohexane.[69] By means of kinetic analysis, the intermediate 1,4-di-*t*-butylcyclohexene, which amounted to about 33% at ~70% conversion, was estimated to desorb from the catalyst surface to the extent as large as 80% at 30°C and 0.084 MPa H_2. *cis*-3,6-Di-*t*-butylcyclohexene amounted only to 1% at the maximum. At low pressures, however, over 80% of the 1,4-di-*t*-butylcyclohexene appeared to be converted to saturated prod-



Scheme 11.2 Hydrogenation pathways of 1,2-di-*t*-butylbenzene to *cis*- and *trans*-1,2-di-*t*-butylcyclohexanes over 5% Rh–C (AcOH; room temperature; 1 atm H_2).

ucts via isomerization to *cis*-3,6-di-*t*-butylcyclohexene, which was hydrogenated faster than the 1,4 isomer. From these results, the hydrogenation pathways of 1,4-di-*t*-butylbenzene over 5% Rh–Al_2O_3 in cyclohexane (30°C and 0.084 MPa H_2) can be estimated as shown in Scheme 11.3.

The differences in the stereoisomeric composition between the estimated and observed values, although not significant, might result from some differences in the stereoisomeric composition of the saturated products that would be produced when 1,4-di-*t*-butylcyclohexene was hydrogenated in the presence or in the absence of 1,4-di-*t*-butylbenzene. At high hydrogen pressures (> 3MPa), the amounts of desorbed intermediates became much smaller, but the amounts of the *trans* saturated product decreased only to slight extents from 11% (100% conversion) at 0.084 MPa to 9.5% (84% conversion) at 15 MPa H_2.

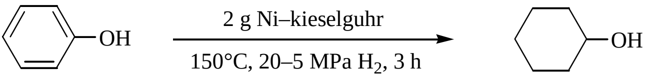


Scheme 11.3 Hydrogenation pathways of 1,4-di-*t*-butylbenzene to *cis*- and *trans*-1,4-di-*t*-butylcyclohexanes over 5% Rh–Al_2O_3 (cyclohexane, 30°C, 0.084 MPa H_2).

11.2 PHENOLS AND PHENYL ETHERS

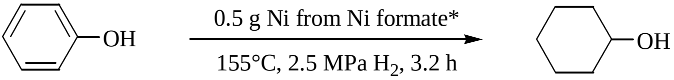
11.2.1 Phenols

The hydrogenation of phenols may proceed more readily than other aromatic compounds under proper use of catalyst and conditions. Over Ni–kieselguhr, hydroxybenzenes such as phenol, catechol, and resorcinol are hydrogenated rapidly at 120–150°C under high pressure. Usually, the yields of the corresponding cyclohexanols are quantitative except for resorcinol, which gave only a 90% yield of cyclohexane-1,3-diol.[70] An example is shown in eq. 11.11 for the hydrogenation of phenol.



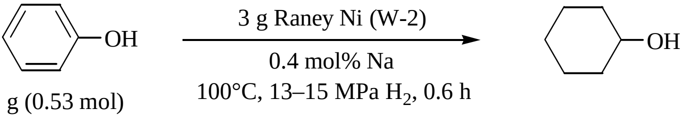
47 g (0.50 mol) quantitative (11.11)

Sasa prepared an effective nickel catalyst for the hydrogenation of phenol by decomposition of nickel formate in a high boiling solvent such as diphenyl ether and diphenyl. The catalyst thus prepared proved more active than Ni–kieselguhr in the hydrogenation phenol (eq. 11.12) and could be used repeatedly more than six times.[71]



50 g (0.53 mol) * Decomposed in diphenyl ether. quantitative (11.12)

Alkaline substances have been used as promoters in the Raney Ni-catalyzed hydrogenation of phenol and alkylphenols.[72,73] The hydrogenations were most effectively promoted by small amounts of anhydrous salts of phenols in the absence of solvents. For example, hydrogenation of 0.53 mol of phenol over 3 g Raney Ni at 100°C and 13–15 MPa H_2 was completed in 0.6 h in the presence of 0.4 mol% of sodium phenoxide (eq. 11.13), compared to ~1 h with addition of 1 ml of 40% aqueous sodium hydroxide, while 3 h or longer was required without an alkaline additive.



50 g (0.53 mol) (11.13)

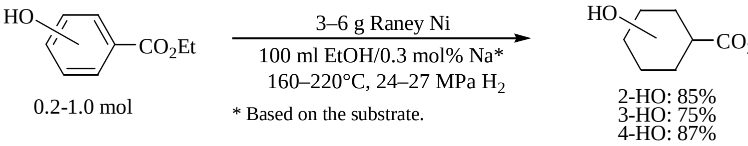
In the absence of alkali, 2,6-dipropylphenol was recovered unchanged and 2,6-diethyl-4-methylphenol underwent hydrogenolysis and hydrogenation to give 1,3-diethyl-5-methylcyclohexane over Raney Ni at temperatures above 300°C. In the presence of alkali, however, both the phenols could be hydrogenated at lower temperatures to give the corresponding cyclohexanols in high yields.[72]

The hydrogenation of phenol or cresols over a nickel catalyst at >250°C under a high hydrogen pressure tends to give the corresponding hydrocarbons rather than the

alcohols as the main product, owing to the hydrogenolysis of the cyclohexanols formed.[74–76] However, the hydrogenolysis of alkylphenols over Ni–kieselguhr at such a high temperature can be depressed by organic bases such as pyridine to give the corresponding cyclohexanols in high yields, without preventing hydrogenation of the benzene ring.[77]

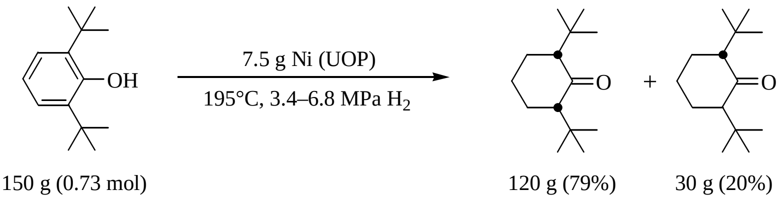
Halophenols are readily hydrogenated to give cyclohexanols by use of Raney Ni–Al alloy in a saturated barium hydroxide solution under mild conditions.[78] For example, when Raney Ni–Al alloy (12 g) was added slowly to a mixture of pentachlorophenol (1.73 g, 6.5 mmol) and a saturated aqueous solution of $Ba(OH)_2$ at 60°C, cyclohexanol was obtained in 91% yield. It has been suggested that halophenols are first hydrogenated to halocyclohexanols and then dehalogenated to give cyclohexanols, since phenol itself gave only a trace amount of cyclohexanol with an almost quantitative recovery of phenol under these conditions.

Hydrogenation of phenolic acids often gives low yields of the corresponding hydroxycyclohexane acids, due to side reactions such as hydrogenolysis of the carbon–oxygen linkage or decarboxylation.[79] High pressure hydrogenations of *p*-hydroxybenzoic acid and its sodium salt over Raney Ni at 200–250°C gave cyclohexanol as the main product and only low yields of 4-hydroxycyclohexanecarboxylic acid.[80] However, in the presence of 0.3 mol% (on the basis of substrate) of sodium ethoxide, the phenolic esters could be hydrogenated at 160–220°C and 24–27 MPa H_2 to give the corresponding hydroxycyclohexanecarboxylic esters in high yields (eq. 11.14).[79]



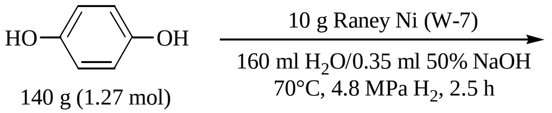
(11.14)

Whitaker found that 6-*t*-butyl-2-methyl- and 4,6-di-*t*-butyl-2-methylphenols could be hydrogenated to the corresponding cyclohexanols, but 2,6-di-*t*-butyl-4-methylphenol added only 2 mol of hydrogen to yield 2,6-di-*t*-butyl-4-methylcyclohexanone over Raney Ni at 140–240°C and 10–17 MPa H_2.[81] Coffield et al. also found that, while 2,6-diisopropylphenol was hydrogenated to give the corresponding cyclohexanol over a nickel catalyst at 200°C, 2,6-di-*t*-butylphenol absorbed only 2 equiv of hydrogen to give the corresponding cyclohexanone and was not hydrogenated to the corresponding cyclohexanol (eq. 11.15).[82]



(11.15)

Among dihydroxybenzenes, catechol[83] and hydroquinone[11] are readily hydrogenated to give almost quantitative yields of the corresponding cyclohexanediols over Ni–kieselguhr in ethanol at 150–175°C. Hydroquinone can be hydrogenated to the diol even at room temperature and 0.1–0.3 MPa H_2 over W-6 Raney Ni in ethanol.[57] Crawford hydrogenated hydroquinone in a 50% water slurry rendered alkaline with sodium hydroxide over W-7 Raney Ni (eq. 11.16).[84]



(11.16)

On the other hand, resorcinol is liable to hydrogenolysis and tends to give decreased yields (65–89%) of cyclohexane-1,3-diol over Ni–kieselguhr, together with 8–22% of cyclohexane and cyclohexanol.[85] The hydrogenolysis products appear to result through the hydrogenation of the cyclohexane-1,3-dione and 3-hydroxycyclohexanone, which may be formed as intermediates and are known to be much more susceptible to hydrogenolysis than the corresponding 1,2- and 1,4-derivatives on hydrogenation.[86]

Hydrogenation of phenols over platinum metals may be accompanied by hydrogenolysis to give deoxygenated products, especially over platinum in acidic media.[87,88] For example, the hydrogenation of phenol over Adams platinum in acetic acid at 25°C and atmospheric hydrogen pressure was accompanied by 35% of hydrogenolysis to give cyclohexane.[20] Iridium and osmium catalysts also show similar high tendency toward the hydrogenolysis of phenolic compounds even in neutral medium.[89–91] Rhodium, ruthenium, and palladium have much lesser tendency toward such hydrogenolysis, although the hydrogenation over palladium usually requires higher temperatures.

Rhodium catalysts are preferred for the hydrogenation of 4-*t*-butylphenol to *cis*-4-*t*-butylcyclohexanol, which is used as an intermediate in perfume industry.[92] In one patent, 4-*t*-butylphenol was hydrogenated over $Rh–TiO_2–BF_3 \cdot OEt_2$ in cyclohexane at 98°C and 1.6 MPa H_2 to give 98% of 4-*t*-butylcyclohexanol containing 81.9% *cis* isomer and 15.9% *trans* isomer.[93] The presence of an acidic substance may favor the formation of the axial (*cis*) alcohol in the rhodium-catalyzed hydrogenation, since 4-*t*-butylcyclohexanone, undoubtedly the most important intermediate in the hydrogenation of 4-*t*-butylphenol, is hydrogenated highly stereoselective toward giving the *cis*-alcohol in the presence of acid.[94] In another patent where 4-*t*-butylphenol was hydrogenated over $Ni–Al_2O_3$ in *i*-butyl acetate, the *cis* isomer represented only 28.1% of the resulting 4-*t*-butylcyclohexanol.[95]

Smith and Stump compared the rate constants and extents of hydrogenolysis in the hydrogenation of hydroxybenzenes over platinum oxide and 5% Rh–C in acetic acid at 30°C and initial hydrogen pressure of approximately 0.34 MPa.[96] The rate constants were calculated on the findings that the hydrogenation was first-order in hydrogen pressure and zero-order in concentration of substrate. It is seen from the results shown in Table 11.7 that hydrogenolysis generally occurs much more extensively over

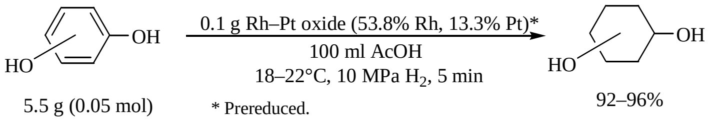
TABLE 11.7 Rate Constants and Extents of Hydrogenolysis for the Hydrogenation of Hydroxybenzenes over Adams Pt and 5% Rh–Al_2O_3 in Acetic Acid[a]

	Rate Constant[b]		H_2 Uptake (mol/mol)[c]	
Compound	Adams Pt	5% Rh–Al_2O_3	Adams Pt	5% Rh–Al_2O_3
Phenol	0.1620	0.0687	3.22 (22)	3.01 (1)
Catechol	0.1330	0.0145	3.63 (31.5)	2.94 (0)
Resorcinol	0.1611	0.0311	4.00 (50)	3.16 (8)
Hydroquinone	0.2072	0.0363	3.97 (48.5)	3.18 (9)
Phloroglucinol[d]	0.0378	0.00807	3.48 (16)	2.85 (0)
Pyrogallol[e]	0.0951	0.00757	3.70 (23)	3.22 (7)

[a]Data of Smith, H. A.; Stump, B. L. *J. Am. Chem. Soc.* **1961**, *83*, 2739. Reprinted with permission from American Chemical Society.
[b]The values were obtained at 30°C and initial hydrogen pressure of ~0.34 MPa, and are given in $l \cdot g\ cat^{-1} \cdot min^{-1}$.
[c]The figures in parentheses indicate the proportions of cleavage of the hydroxyl groups in a molecule in percent.
[d]1,3,5-Benzenetriol.
[e]1,2,3-Benzenetriol.

Adams platinum than over 5% Rh–Al_2O_3. Resorcinol and hydroquinone hydrogenate faster than catechol over both platinum and rhodium catalysts. In particular, it is noted that, over platinum, resorcinol and hydroquinone hydrogenate as fast as or even faster than phenol, and, at the same time, the proportions of hydrogenolysis with these dihydroxybenzenes are much greater than with phenol and catechol.

Zymalkowski and Strippel hydrogenated dihydroxybenzenes with only slight hydrogenolysis over rhodium–platinum oxide in acetic acid at room temperature and 10 MPa H_2 and obtained the corresponding cyclohexanediols in 92–96% yields (eq. 11.17).[97] The hydrogenations at atmospheric pressure required much longer reaction times, and the yield of cyclohexanediol decreased to 86% with resorcinol. The proportions of *cis* isomer in the cyclohexanediols obtained at 10 MPa H_2 were 81% from catechol, 68% from resorcinol, and 68% from hydroquinone and always greater than those obtained at atmospheric pressure (75, 49, and 52%, respectively).

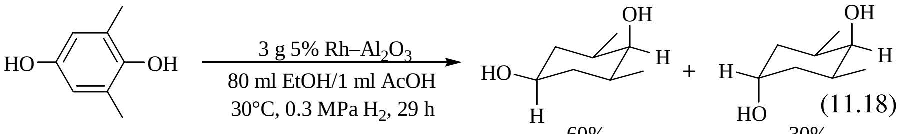


(11.17)

Rylander and Himelstein studied the hydrogenation of resorcinol over supported platinum, palladium, rhodium, and palladium–rhodium as catalysts in ethanol at 65°C and an initial hydrogen pressure of 0.34 MPa. Extensive hydrogenolysis to give cyclohexanol took place over 5% Pt–C, 5% Pd–C, and 2.5% Pd–2.5% Rh–C, and the yields of cyclohexane-1,3-diol were only 18.7–26.2%. Rhodium catalysts caused hydro-

genolysis to much lesser extents, although hydrogenation over 5% Rh–C still resulted in considerable hydrogenolysis to give 30% yield of cyclohexanol. The best results were obtained over 5% Rh–Al_2O_3, which yielded 93% of cyclohexane-1,3-diol together with 7% of cyclohexanol, although in another experiment with the same catalyst cyclohexanol was formed in 16% yield.[98]

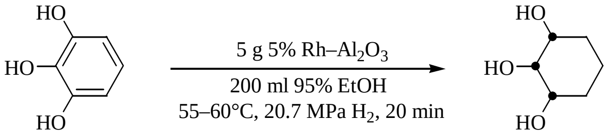
Hydrogenation of 2,6-dimethylhydroquinone over 5% Rh–Al_2O_3 in ethanol containing a small amount of acetic acid at 30°C and 0.3 MPa H_2 gave a nearly quantitative yield of a mixture of the corresponding *cis*- and *trans*-cyclohexane-1,4-diols, mostly with all-*cis* configuration with respect to the 2,6-dimethyl and 1-hydroxyl groups (eq. 11.18).[99] Hydrogenation of the corresponding quinone in ethanol over Raney Ni at 180°C and 3.4 MPa H_2 was not satisfactory. The product was a complex mixture, and purification resulted in a low yield (14%) of the cyclohexanediols.[100]



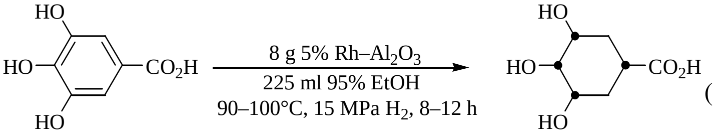
10.9 g (0.079 mol)   60%   30%   (11.18)

+ small amounts of other products (presumably isomeric diols)

The usefulness of rhodium catalysts is also seen in the hydrogenation of pyrogallol (eq. 11.19)[101] and gallic acid (eq. 11.20)[102] over 5% Rh–Al_2O_3 in ethanol. The all-*cis* products were also obtained in higher yields than with supported palladium, platinum, or ruthenium catalysts.



40 g (0.32 mol)   26 g (62%)   (11.19)



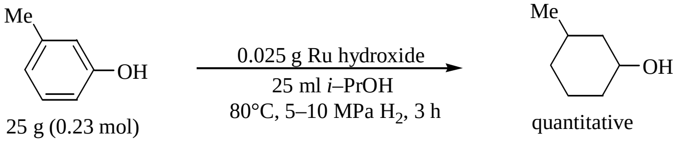
50 g (as monohydrate , 0.266 mol)   (11.20)

21–24 g (45–51%)
18–20 g (38–43%) after recryst.

Angyal et al. obtained an improved yield (31%) of *cis*-inositol, an interesting compound forming strong complexes with metal ions, by hydrogenating tetrahydroxyquinone over a large amount (i.e., more Pd than substrate) of freshly reduced palladium hydroxide in water in the pH range of 3.5–7.0 at room temperature and atmospheric pressure. Tetrahydroxyhydroquinone is first hydrogenated rapidly to give hexahy-

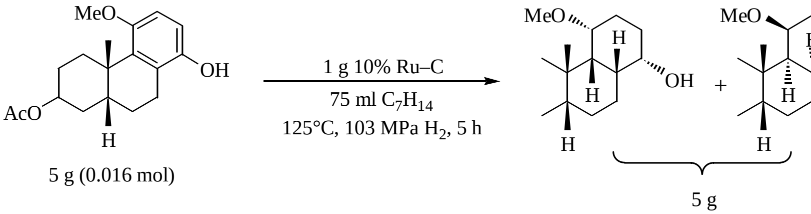
droxybenzene. The use of chromatography on cation-exchange resins in the calcium form facilitated the separation of *cis*-inositol from the products.[103]

Ruthenium catalysts have been shown to be highly effective for the hydrogenation of phenols without accompanying hydrogenolysis.[104] Equation 11.21 is an example showing how small an amount of ruthenium catalyst is sufficient for complete hydrogenation of a phenol within a reasonable time (*m*-cresol : Ru hydroxide = 1000 : 1).[105]



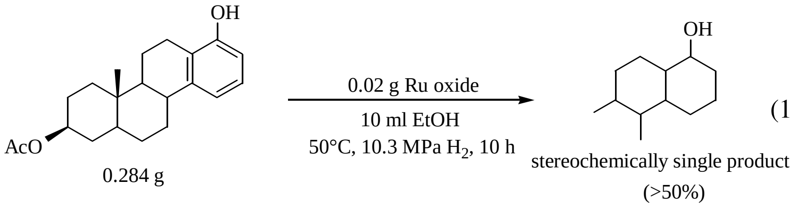
(11.21)

Equation 11.22 is an example showing poor tendency toward hydrogenolysis as well as high stereoselectivity of ruthenium catalyst in the hydrogenation of a phenol or phenyl ether derivative.[106]



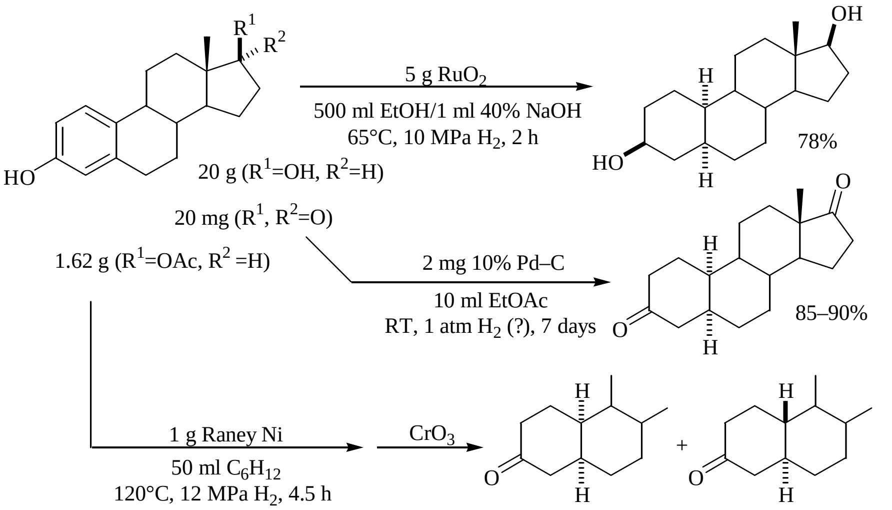
(11.22)

High stereoselectivity of ruthenium catalyst without accompanying hydrogenolysis in a phenol hydrogenation is also seen in the examples shown in eq. 11.23[107] and Scheme 11.4. In the case of eq. 11.23, the hydrogenation over platinum oxide in acetic acid resulted in extensive hydrogenolysis.The hydrogenation without hydrogenolysis was also possible with use of Raney Ni in the presence of potassium hydroxide, but the product was a complex mixture of the stereoisomers.



(11.23)

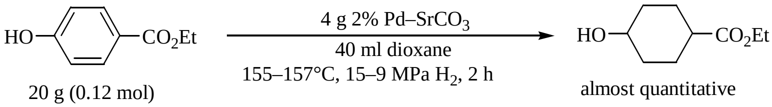
Hydrogenation of estrone and β-estradiol over ruthenium dioxide gave the 5α,10α-isomer (*cis–syn–trans*) in high yields,[108,109] of the four possible steric arrangements for the A/B rings (the *trans–syn–trans* arrangement, which would require a boat form for the B ring, is considered to be unfavorable), while the hydrogenation of estradiol 17-acetate over Raney Ni in cyclohexane gave a mixture of the 5α,10α and 5α,10β isomers in about equal amounts.[110] The hydrogenation over Pd–C did not proceed to



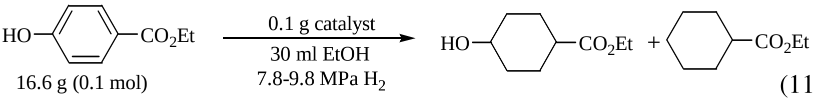
Scheme 11.4 Hydrogenation of estrone and its derivatives.

the diol and gave the 5α,10α-dione in high yield (Scheme 11.4).[111] The hydrogenation over platinum oxide was accompanied by extensive hydrogenolysis.[110,112]

Palladium catalysts are known to be effective for the hydrogenation of phenols with minimum amounts of accompanying hydrogenolysis, although higher reaction temperatures are usually required.[80,113] An exception to this generalization is the hydrogenation of resorcinol where as much extensive hydrogenolysis as with 5% Pt–C occurred over 5% Pd–C in ethanol at 65°C and 0.34 MPa H_2 to give only a 20.5% yield of cyclohexane-1,3-diol.[98] Equation 11.24 shows an example of a poor tendency of palladium catalyst toward hydrogenolysis in phenol hydrogenation in the hydrogenation of ethyl *p*-hydroxybenzoate over 2% Pd–$SrCO_3$.[113] It is noted that the same selective hydrogenation can also be achieved successfully either over rhodium oxide at 50–65°C or over ruthenium dioxide at 95–100°C under 7.8–9.8 MPa H_2 (eq. 11.25).[114]

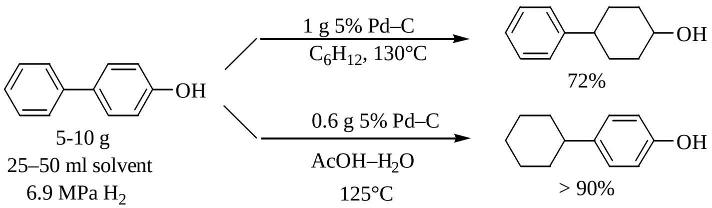


(11.24)



(11.25)

Catalyst	Additive	T (°C)	Time (h)	Product (%) (GC)	
Rh oxide	AcOH 0.05 ml	55–65	0.5	98 (87% *cis*, 13% *trans*)	2
Ru oxide	10% AcOH 0.5 ml	95–100	1.25	96 (84% *cis*, 16% *trans*)	4



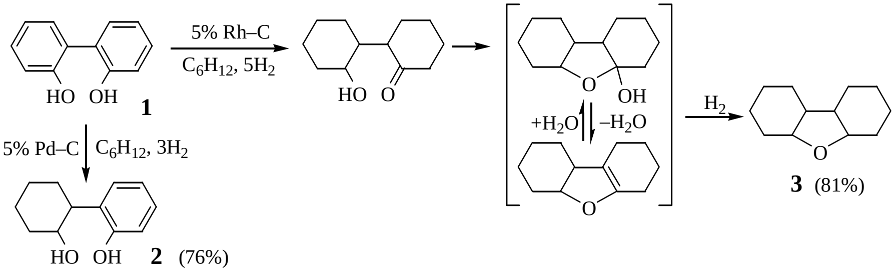
Scheme 11.5 Selective hydrogenation of 4-phenylphenol over Pd–C.

Selective hydrogenation of 4-phenylphenol to either 4-phenylcyclohexanol or 4-cyclohexylphenol was best achieved over Pd–C of the platinum metal catalysts investigated.[55] In water–acetic acid, 4-cyclohexylphenol was formed in yields greater than 90%, while 4-phenylcyclohexanol was formed in 53–72% yield in cyclohexane (Scheme 11.5). Hydrogenolysis was an important side reaction over Pt–C and Ir–C. Ru–C and Rh–C showed a greater tendency to give 4-cyclohexylcyclohexanol, although very little hydrogenolysis occurred over these catalysts. The high selectivity to 4-cyclohexylphenol in water–acetic acid has been explained by assuming that the phenol ring was more strongly solvated and hence more weakly adsorbed on the catalyst surface than in cyclohexane solvent.[115]

Musser and Adkins hydrogenated 2-, 3-, and 4-hydroxybiphenyls and their ethers over Raney Ni at 130–140°C and over copper–chromium oxide at 225–240°C under 10–20 MPa H_2 in dioxane or dry ethanol.[116] Over Raney Ni, the unsubstituted benzene ring was hydrogenated preferentially in the case of 4-hydroxybiphenyl and its ethers, while in 2-hydroxybiphenyl and its ethers and 3-hydroxybiphenyl the oxygenated ring was more reactive toward hydrogenation. In 3-alkoxybiphenyl, both the rings were hydrogenated at nearly the same rate. Over copper–chromium oxide, a much greater tendency to hydrogenate in the hydroxy-substituted ring was observed with 4-hydroxybiphenyl. Over Ni–kieselguhr at 200°C, considerable hydrogenolysis occurred in the hydrogenation of 4,4′-dihydroxybiphenyl and its dimethyl ether; 4-hydroxy- and 4-methoxybicyclohexyl were obtained in 20 and 50% yields, respectively.[117]

Rylander and Steele found that over Pd–C catalyst, *o*,*o*′-dihydroxybiphenyl (**1**) was selectively hydrogenated to *o*-(2-hydroxycyclohexyl)phenol (**2**) in high yield, while over Rh–C, perhydrodibenzofuran (**3**) was produced in a high yield of 81%, probably through the reaction pathways shown in Scheme 11.6.[118]

Hydrogenation of phenol and alkylphenols over iridium catalysts is often accompanied by rather extensive hydrogenolysis even in a neutral solvent, in a similar manner as with platinum in acidic medium. Rylander and Steele observed that the hydrogenation of 3,5-dimethylphenol over 5% Ir–C in isopropyl alcohol at 100°C and 5.2 MPa H_2 afforded 1,3-dimethylcyclohexane in 76% yield, compared to 25% yield over 5% Pt–C in acetic acid-hydrochloric acid.[89] Similarly, 2,5-dimethylphenol caused 60% of hydrogenolysis to give 1,4-dimethylcyclohexane over the iridium catalyst in isopropyl alcohol, compared to 67% over 5% Pt–C in acetic acid-hydrochloric acid.[119] Table 11.8 compares the extents of accompanying hydrogenolysis when phe-



Scheme 11.6 Hydrogenation of *o*,*o*′-dihydroxybiphenyl over Pd–C and Rh–C catalysts.

nol and methyl-substituted phenols were hydrogenated over an iridium black in *t*-butyl alcohol at 80°C and 4.9 MPa H_2.[120] The degree of hydrogenolysis depended greatly on the final pH of the water in which iridium hydroxide was precipitated from an iridium chloride solution with lithium hydroxide, although the iridium hydroxide was prereduced with hydrogen in water at 120°C and 4.9 MPa H_2 and carefully washed with water, and, further, the reduction and washing process was repeated until the water after the reduction became neutral. For example, the extent of hydrogenolysis of *p*-cresol varied from 15.3% over the catalyst obtained from a slightly alkaline medium of precipitation to 48% over the catalyst obtained from a slightly acidic medium. It was also observed that the proportion of hydrogenolysis increased slightly with increasing hydrogen pressure over the acidic catalyst from 44% at 0.1 MPa H_2 to 58%

TABLE 11.8 The Amounts (and *Cis/Trans* Isomer Ratios) of Hydrogenolysis Product in Hydrogenation of Phenol and Methyl-Substituted Phenols over Iridium Catalyst[a,b]

Phenol	Proportion of Hydrogenolysis (mol%)[c]	*Cis/Trans* Isomer Ratio of Dimethylcyclohexane[c]
Unsubstituted	11.7	—
2-Methyl-	5.5	—
3-Methyl-	20.9	—
4-Methyl-	30.9	—
2,3-Dimethyl-	13.1	42.7
2,4-Dimethyl-	4.0	2.2
2,5-Dimethyl-	5.4	5.4
2,6-Dimethyl-	2.2	4.5
3,4-Dimethyl-	20.7	68
3,5-Dimethyl-	37.7	9.8

[a]Fukui, S.; Nishimura, S. Unpublished results.

[b]The substrate (0.5 ml) was hydrogenated over 5 mg of iridium black in 7 ml *t*-BuOH at 80°C and 4.9 MPa H_2. The same catalyst, prepared from the iridium hydroxide precipitated at pH 7, was used throughout the experiments.

[c]The products were analyzed by GC at 88–100% conversion. Small amounts, if any, of cyclohexanones in the products were accounted for as an unhydrogenolyzed product, since the ketones are usually susceptible to hydrogenolysis to much lesser extents over iridium (see Nishimura, S. et al., Ref. 91).

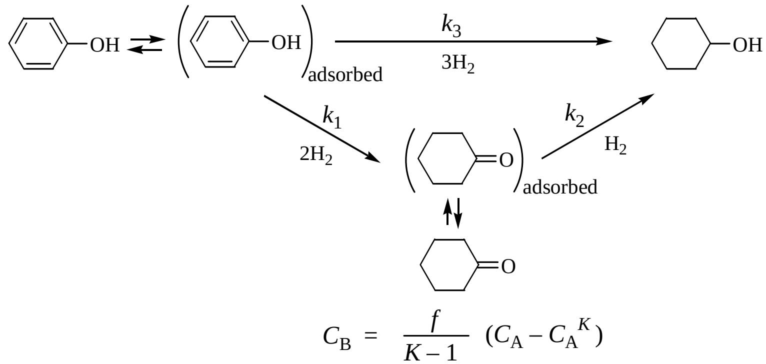
at 9.8 MPa H_2, while the reverse was true with the catalyst from neutral or alkaline medium. The results of Table 11.8 clearly indicate that the hydrogenolysis is depressed by the methyl group located at an *ortho* position of the hydroxyl group. The *ortho* methyl group effect is most pronounced in 2,6-dimethylphenol where the amount of hydrogenolysis was only 2.2%. On the other hand, considerable amounts of hydrogenolysis always occur in the phenols without any methyl substituent at the *ortho* positions; the largest amount of hydrogenolysis (37.7%) was obtained with 3,5-dimethylphenol. It is noted that the *cis/trans* isomer ratio of the dimethylcyclohexanes formed by hydrogenolysis is definitely greater in the *gem*-dimethyl substituted phenols, 2,3- and 3,4-dimethylphenols, than in the other dimethylphenols.

Bisphenol A, 2,2-bis(4-hydroxyphenyl)propane, was selectively hydrogenated over Ni–kieselguhr in dioxane in the presence of triethylamine at 100°C and 2.45 MPa H_2 to give a product containing 93% of 2-(4-hydroxycyclohexy)-2-(4-hydroxyphenyl)propane, a useful material or modifier for fibers and resins, with 100% conversion (see Section 11.1.2).[121] Hydrogenation of bisphenol A to the perhydro compound was accomplished over 2% Ru–Al_2O_3 in 2-octanol at 180°C and 3.9 MPa H_2 to give a 94.5% yield.[122]

11.2.2 Hydrogenation to Cyclohexanones

It has been known that cyclohexanones are formed as intermediates in the hydrogenation of phenols.[83,88,123,124] However, the amounts of the ketone intermediates accumulated during the hydrogenation depend greatly on the nature of catalysts and reaction conditions, as well as on the structure of phenols.

The amount of cyclohexanone desorbed from the catalyst surface during hydrogenation can be conveniently obtained by applying the equation derived on the basis of the reaction pathways shown in Scheme 11.7, where C_A and C_B are the concentrations of phenol and cyclohexanone, respectively, when the initial concentration of phenol is taken as unity, f is the fraction of cyclohexanone desorbed from the catalyst



$$C_B = \frac{f}{K-1}\left(C_A - C_A^{\,K}\right)$$

Scheme 11.7 Hydrogenation pathways of phenol and an expression showing the variation in concentration of the intermediate cyclohexanone in the course of hydrogenation.

surface, and K is a constant related to the relative reactivity of cyclohexanone versus phenol.[124,125]

When an adsorption–desorption equilibrium is attained with respect to phenol as well as the intermediate ketone, f is expressed by $k_1/(k_1 + k_3)$ and its value represents the true fraction of phenol that is hydrogenated via cyclohexanone as intermediate. Coussemant and Jungers studied the hydrogenation of phenol over Raney Ni at 113–174°C and 4 MPa H_2 and concluded that all of phenol was hydrogenated via cyclohexanone as intermediate, although the maximum mol fraction of cyclohexanone in the reaction mixture was only 0.18 at 174°C and 0.12 at 113°C over a preparation of Raney Ni.[124] The low values result from a high reactivity of cyclohexanone versus phenol. The ratio k_2/k_1 was 1.95 at 174°C and 3.0 at 113°C, and the value of the relative reactivity K was 3.4 at 174°C and 5.9 at 113°C. The smaller values of K at higher temperatures accounted for increased maximum yields of cyclohexanone with increasing temperature. The ratio of adsorption coefficients b_2/b_1, which was evaluated by using the results on the hydrogenation of cyclohexanone, was found to vary from 1.8 to 1.6 over the temperature range of 113–174°C.

Takagi et al. applied the equation in Scheme 11.6 to the hydrogenation of *o*-, *m*- and *p*-cresols over ruthenium, rhodium, and Pd–C at 80°C (120°C for Pd–C) and 7.8–9.8 MPa H_2, based on a quantitative analysis of the reaction mixture by means of gas chromatography.[126,127] The results are summarized in Table 11.9.

It is seen that, over all the three metals, the amounts of methylcyclohexanone intermediates desorbed from the catalyst surface do not differ much between the three

TABLE 11.9 The Selectivities for the Formation of Cyclohexanone Intermediates in the Hydrogenation of Isomeric Cresols and the Relative Reactivities of the Ketone to Cresol over Ru, Rh, and Pd–C Catalyst[a,b]

Cresol	Catalyst	Selectivity to Ketone Intermediate Desorbed (f)[c]	Relative Reactivity of Ketone to Cresol (K)[c]
Ortho	Ru	0.77	0.98
Ortho	Rh	0.55	0.07
Ortho	Pd–C	1.0	0.94
Meta	Ru	0.61	2.25
Meta	Rh	0.52	0.25
Meta	Pd–C	1.0	1.07
Para	Ru	0.60	3.50
Para	Rh	0.54	0.30
Para	Pd–C	1.1	1.60

[a]Data of Takagi, Y.; Nishimura, S.; Hirota, K. *J. Catal.* **1968**, *12*, 214; *Bull. Chem. Soc. Jpn.* **1970,** *43*, 1846. Reprinted with permission from Academic Press Inc. and from Chemical Society of Japan, respectively.
[b]Cresol (0.1 mol) was hydrogenated without solvent over 0.02 g of Ru or Rh hydroxide at 80°C or 0.3 g of 5% Pd–C at 120°C under 7.8–9.8 MPa H_2.
[c]The values of f and K were determined by finding the most suitable sets of them for the equation in Scheme 11.7 to represent the varying concentration of the ketone intermediate during the course of hydrogenation.

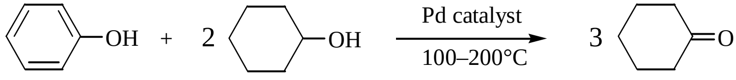
cresol isomers and were estimated to be 60–77% over Ru, 52–55% over Rh, and 100% over Pd–C. The values for rhodium catalyst were in fairly good accord with those obtained previously by using stereochemical and extrapolation methods.[128] The relative reactivity of the ketone versus cresol, K, always increases in the order *ortho* < *meta* < *para* with respect to the isomers and Rh < Pd–C < Ru, with respect, in turn, to the catalyst metals. The quantitative formation of methylcyclohexanones over Pd–C ($f = 1.0$) indicates that the adsorption–desorption equilibrium with respect to the intermediate ketone has been fully attained during the course of hydrogenation. Matsumoto et al. also observed nearly quantitative formation (97.3%) of cyclohexanone in the hydrogenation of phenol over a Pd–C in acetic acid at 50°C and atmospheric hydrogen pressure.[129] The selectivity to cyclohexanone (see figures in parentheses) depended on the solvent used: acetic acid (97.3) > cyclohexane (94.4) ≥ dioxane (94.3) > 1-butanol (12.1). The results in Table 11.9 with ruthenium and rhodium catalysts indicate that nearly one-third or more of cresols were hydrogenated not via methylcyclohexanones as intermediates, on the assumption that the desorption–adsorption equilibrium for the ketone intermediate, as observed over Pd–C, was also attained over these catalysts, as would be probable from consideration of the values of K. For the results obtained with ruthenium and rhodium catalysts, it has been suggested that the fractions of the ketones formed from cresols over these catalysts are not much different from 67%, the value that is deduced by assuming that all kinds of possible dihydrocresols are produced in equal amounts on the catalyst surface, and then the unsaturated ketones or their enols among the dihydrocresols are hydrogenated preferentially to the saturated ketones and the other dihydrocresols (unsaturated alcohols) to methylcyclohexanols.[128] Over the third-row group VIII metals, Os, Ir, and Pt, the detectable amounts of the ketone during hydrogenation were small and an estimation of the desorbed ketone intermediate by application of the equation in Scheme 11.7 appeared to result in a considerable error.[90] The values of K for these metals were greater than those for the second-row group VIII metals, and hence it appeared to be difficult to estimate the true selectivity to the ketone intermediate from cresols over these metals, since a significant part of the ketone formed on the catalyst surface might be hydrogenated to the alcohol without leaving the surface over these metals.

Higashijima and Nishimura studied the factors affecting the formation of cyclohexanone intermediates in the hydrogenation of phenols over 5% Pd–C catalysts of alkaline (Pd–C and Pd–C B), neutral (Pd–C N), and acidic (Pd–C A) nature.[130,131] The varying composition of the reaction mixture versus reaction time has been analyzed by a computer simulation to obtain the values of f and K as well as the related kinetic constants on the basis of a Langmuir–Hinshelwood model according to the reaction routes described in Scheme 11.7.[130,131] Regardless of the difference in the nature of the catalysts, the hydrogenation of *p*-cresol in cyclohexane at 80°C and in the range of hydrogen pressure from 0.15 to 5–8 MPa gave always high selectivities for the formation of the ketone intermediate ($f = 0.85$–1.0). The value of K, however, increased greatly with increasing hydrogen pressure. Thus, for the change in hydrogen pressure from 0.15 to 5.0 MPa, the value increased from 0.047 to 0.46 over Pd–C, from 0.082 to 0.26 over Pd–C B, from 0.026 to 0.32 over Pd–C N, and from 0.014 to 0.093 over

Pd–C A. The increases in the value of K with hydrogen pressure have been shown to be due largely to the corresponding increases in the rate of hydrogenation of the ketone (k_2) with hydrogen pressure, since the effect of hydrogen pressure on the rates of hydrogenation of cresol ($k_1 + k_3$) was found to be rather small. The very small values of K over Pd–C N and Pd–C A were found to be due largely to extremely small values of the relative adsorption equilibrium constant of the ketone to cresol (b_2/b_1) over these catalysts (0.011–0.018 for Pd–C N and 0.004–0.008 for Pd–C A), which have been obtained by the relationship: $K = k_2b_2/(k_1 + k_3)b_1$ and also from the results of the competitive hydrogenations of the ketone and the cresol. The greater values of K with increased hydrogen pressures result in decreased yields of the ketone intermediate at the maximum, which is given by $f \times C_B^{K/(1-K)}$. The highest maximum yield of the ketone intermediate, 88.4% at 98% conversion, was obtained over Pd–C A at 0.15 MPa H_2, which decreased to 67.0% at 5 MPa H_2. In alcoholic solvents, the maximum yields of the ketone intermediates as well as the rates of hydrogenation of phenols decreased, compared to those obtained in hydrocarbon solvents. The degrees of the decrease were much greater for Pd–C than for Pd–C A. From the results it has been suggested that an alcoholic solvent may weaken the adsorption of phenols by an interaction with the hydroxyl group of phenols, the degree of which would become greater by the formation of the phenoxide ion over a basic catalyst.[131] It is noted that a similar interaction of hydroxylic solvents with the phenol ring has been suggested by Rylander for the explanation of different selectivity between a hydroxylic solvent and cyclohexane in the hydrogenation of 4-hydroxybiphenyl over Pd–C (see Ref. 8, p 341 and Scheme 11.5).

A kinetic model of the hydrogenation of 2-*t*-butylphenol to *cis*- and *trans*-2-*t*-butylcyclohexanol via desorbed and not desorbed 2-*t*-butylcyclohexanone as the intermediate has been studied by Kut et al., together with the study on the thermodynamic equilibrium of the system 2-*t*-butylphenol/2-*t*-butylcyclohexanone/*cis*- and *trans*-2-*t*-butylcyclohexanol and hydrogen, over various transition metals at temperatures between 100 and 280°C and hydrogen pressures of 1–10 MPa.[132,133] A kinetic study on the hydrogenation of 4-*t*-butylphenol was also reported by Murzin et al. with Rh–C in hexane at 40–100°C and 0.4–4 MPa H_2.[92]

A number of patents have been applied for the synthesis of cyclohexanone by hydrogenation of phenol where palladium catalysts have been employed.[134] The presence of basic components such as CaO, MgO, and Na_2CO_3 has often been claimed to be effective for this purpose. As an example, 1000 parts of phenol was hydrogenated over 1 part of Pd–C containing 0.01 part of Na_2CO_3 and 5000 ppm of Na in a 16.5% solution of aqueous ethanol at 186°C and 0.48 MPa H_2 for 2.5 h to give a mixture of 97.2% of cyclohexanone, less than 0.5% of phenol, and cyclohexanol.[134a] In another patent, the reaction of 1 mol of phenol and 2 mol of cyclohexanol to give 3 mol of cyclohexanone was carried out over a palladium catalyst at 100–200°C (eq. 11.26).[135]

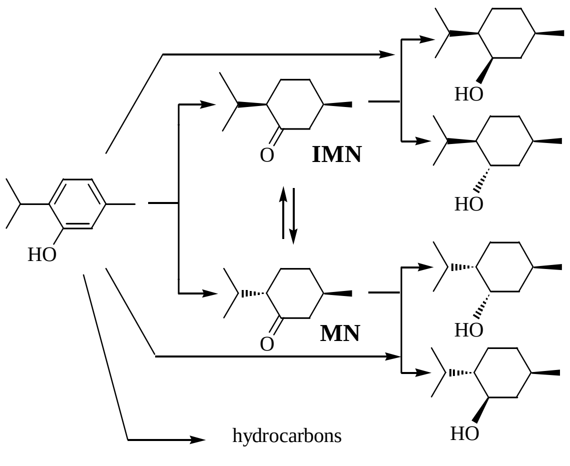


(11.26)

4-*t*-Butylphenol was hydrogenated without solvent over Pd–C at 100–115°C and 0.049 MPa H_2 in the presence of sodium carbonate to give 4-*t*-butylcyclohexanone in 94.0% selectivity, compared to 80.2% selectivity at 0.49 MPa H_2.[136]

Besson et al. studied the hydrogenation of thymol in cyclohexane at 40–100°C and 3 MPa H_2 over Pt–C (4.18% Pt), Rh–C (4.0% Rh), and Ir–C (2.24% Ir), which were prepared by an ion exchange with $Pt(NH_3)_4^{2+}$, $Rh(NH_3)_5^{3+}$, and $Ir(NH_3)_5^{3+}$ cations on charcoal previously functionalized by NaClO oxidation,[137] followed by reduction with flowing hydrogen at 300°C.[138] Over Pt–C and Rh–C the hydrogenation via the ketone intermediates, isomenthone (IMN) and menthone (MN), was the predominant route (see Scheme 11.8). The initial selectivities to IMN and MN were 50 and 20% over Pt–C, and 60 and 15% over Rh–C, respectively. The IMN and MN are hydrogenated to the alcohols only slowly over both the catalysts as a result of the steric hindrance effect of the isopropyl group to the C=O hydrogenation. In particular, over Rh–C they accumulate in the reaction medium up to a maximum value of 75% at nearly complete conversion of thymol. Further, the isomerization of IMN to MN was found to occur over Rh–C when thymol had been completely converted. In contrast to the hydrogenation over the platinum and rhodium catalysts, much smaller amounts of the ketone intermediates (~6%) and larger amounts of hydrogenolysis products (≤11% of *p*-menthane at 60°C, compared to < 2% with Rh–C, and *p*-isopropyltoluene) were detected in the hydrogenation over Ir–C. Since the iridium catalyst has a relatively low activity for the hydrogenation of the ketones, it has been suggested that the direct hydrogenation of thymol to the menthols is the most favored route on iridium catalyst.

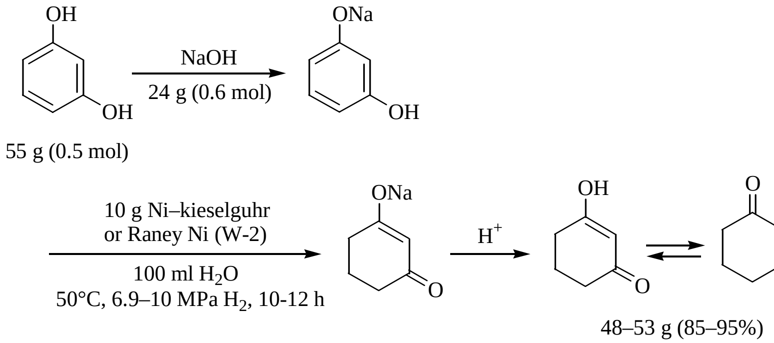
Konuspaev et al. studied the hydrogenation of thymol over Ni-based catalysts.[139] The effects of the catalyst support and the solvent on the *cis-trans* isomerization of the intermediate ketones, which governed the stereoselectivity, have been examined. Allakhverdiev et al. hydrogenated thymol with the catalysts modified by inorganic com-



Scheme 11.8 Hydrogenation of thymol and the ketone intermediates.

pounds containing chloride ion, which was responsible for the poisoning effect even after the reduction of catalysts.[140] The modifiers influenced the rate of keto–enol transformation which was thought to be the key step governing the selectivity and stereoselectivity.

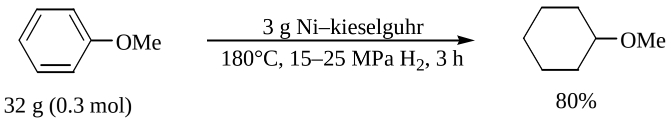
Resorcinol as mono sodium salt is selectively hydrogenated over Ni–kieselguhr to the sodium salt of dihydroresorcinol, which on acidification gives cyclohexane-1,3-dione in high yield (eq. 11.27).[141,142] The same selective hydrogenation [10 g (0.091 mol) resorcinol] was performed with 5% Rh–Al_2O_3 (2.0 g) in 20 ml of water containing 4.36 g (0.109 mol) of NaOH at room temperature and an initial H_2 pressure of 0.34 MPa to give 8.90 g (87.4% yield) of dihydroresorcinol.[96,143]



(11.27)

11.2.3 Phenyl Ethers

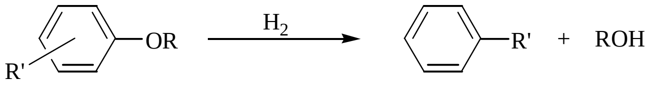
The hydrogenation of phenyl ethers, unlike that of phenols, is not promoted in the presence of alkali, and is usually more susceptible to hydrogenolysis than in phenols at the ether linkage. In general, the ease of hydrogenolysis of Ar-OR linkage increases with respect to the OR group: OEt < OMe < OCH_2O < OAr.[11,144] Thus, the hydrogenation of anisole over Ni–kieselguhr at 180°C and 15 MPa H_2 gave an 80% yield of methoxycyclohexane (eq. 11.28), while the hydrogenation of diphenyl ether under the same conditions afforded dicyclohexyl ether in only 40% yield. Even more extensive hydrogenolysis may occur in the hydrogenation over Raney Ni. For example, with Raney Ni the yield of methoxycyclohexane from anisole was 66%, compared to 80% with Ni–kieselguhr, and diphenyl ether gave only a 14% yield of cyclohexyl phenyl ether, together with cyclohexane and cyclohexanol.[144]



(11.28)

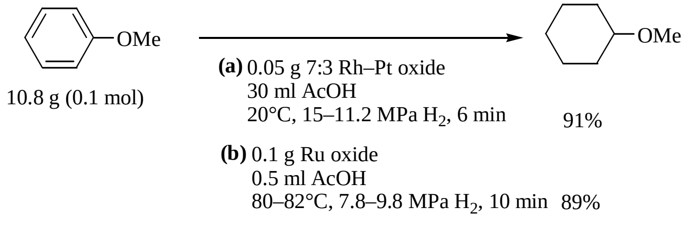
With the platinum group metals, the hydrogenolysis of aryl ethers, in general, tends to occur more extensively over osmium, iridium, and platinum (the third-row metals) than over ruthenium, rhodium, and palladium (the second-row metals).[145,146] The

cleavage of an alkyl aryl ether usually takes place during the course of saturation of the benzene ring. However, apparently direct cleavage of the aryl–oxygen linkage to give the corresponding arene and alcohol as shown in eq. 11.29 may also occur, particularly over platinum. This type of hydrogenolysis may contribute to rather extensive hydrogenolysis of aryl ethers over this metal. For example, such a direct cleavage was found to occur to an extent of 9.5% in the hydrogenation of *p*-ethoxytoluene over platinum in ethanol at 50°C and atmospheric hydrogen pressure.[146] Even more extensive hydrogenolysis (~21%) took place in the hydrogenation of the corresponding *meta* isomer.[147]



(11.29)

Smith and Thompson observed that extensive hydrogenolysis (40–60%) of the methoxyl group occurred in the hydrogenation of mono-, di-, and trimethoxybenzenes over Adams platinum in acetic acid at 30°C and the initial hydrogen pressure of 0.28–0.41 MPa but was much lesser (6–18%) over 5% Rh–Al_2O_3.[148] Use of an alcoholic solvent, especially methanol or ethanol, should be avoided in the hydrogenation of aryl ethers, since an enol ether intermediate may react with the alcohol to afford an acetal, which is usually hydrogenated less readily.[146] The presence of water may lead to the formation of cyclohexanones, which result from the hydrolysis of the enol ether intermediates, although ease of the hydrolysis depends greatly on the nature of the catalyst and the reaction conditions. Ruthenium, rhodium, and rhodium–platinum catalysts can catalyze the hydrogenation of aryl ethers under mild conditions and are preferred for avoiding accompanying hydrogenolysis. Examples are shown in eqs. 11.30[24,114] and 11.31.[145]



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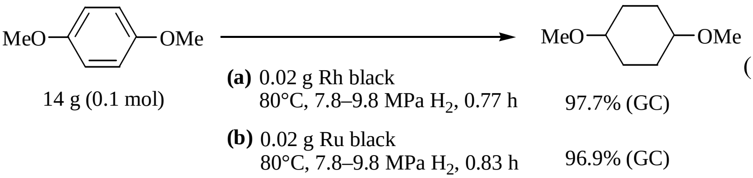


(11.31)

In the hydrogenation of the three isomeric dimethoxybenzenes over the platinum group metals, the *meta* isomer hydrogenolyzed to greater extents and gave smaller *cis/trans* isomer ratios of dimethoxycyclohexanes than the *ortho* and *para* isomers with only one exception with osmium, where the *para* isomer underwent slightly more hydrogenolysis than the *meta* isomer (Table 11.10). It is of interest that the greater ten-

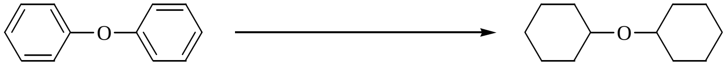
TABLE 11.10 Proportions of Hydrogenolysis and *Cis*-Isomer Formation in Hydrogenation of Isomeric Dimethoxybenzenes over Platinum Metal Catalysts[a,b]

	Hydrogenolysis (mol%)[c]			% *Cis* Isomer in Dimethoxycyclohexane		
Catalyst	*Ortho*	*Meta*	*Para*	1,2-	1,3-	1,4-
Ru	1.6	17.5	2.4	82	73	80
Rh	1.2	9.4	2.0	87	67	81
Pd–C	3.3	17.0	4.9	86	56	64
Os	5.5	15.0	19.8	90	73	80
Ir	8.0	30.4	21.3	92	77	82
Pt	4.0	9.5	8.1	91	73	81

[a]Data of Takagi, Y.; Ishii, S.; Nishimura, S. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 917. Reprinted with permission from Chemical Society of Japan.
[b]Dimethoxybenzene (10.4 g, 0.1 mol) was hydrogenated over 0.02 g of unsupported metal at 80°C or over 0.2 g of 5% Pd–C at 120°C under 7.8–9.8 MPa H_2.
[c]Given by mol% (methoxycyclohexane + 2 × cyclohexane) in saturated product.

dency of the *meta* isomer toward hydrogenolysis is more pronounced over the second-row metals (Ru, Rh, Pd), where the amounts of hydrogenolysis in the *para* isomer were as small as those in the *ortho* isomer.[145]

As with nickel catalysts, the hydrogenation of phenyl ether over platinum group metals is also accompanied by considerable amounts of hydrogenolysis, resulting in decreased yields of cyclohexyl ether. Rylander and Kilroy compared the six carbon-supported platinum metal catalysts (5% metal) in the hydrogenation of phenyl ether in ethanol at room temperature.[149] At 6.9 MPa H_2, the yield (%) of cyclohexyl ether (given in parentheses) decreased in the order Pd–C (90) > Ir–C (60) > Rh–C (50), Ru–C (50), Os–C (50) > Pt–C (40). At atmospheric pressure, yields over Rh–C and Pt–C further decreased to 21 and 14%, respectively. The highest yield over Pd–C is noteworthy, although the rate was the smallest over Pd–C ($\frac{1}{270}$th of the rate over Rh–C). The unusually high selectivity of Pd–C for cyclohexyl ether probably results from a characteristic nature of palladium to selectively produce the enol ether intermediates from phenyl ethers,[146] just as cyclohexanone intermediates are selectively formed over this metal in the hydrogenation of phenols. The enol ethers are usually hydrogenated with little hydrogenolysis over palladium catalysts.[150] Phenyl ether can also be hydrogenated to cyclohexyl ether in high yields over 7:3 rhodium–platinum oxide[114] or rhodium hydroxide[26] with addition of small amounts of acetic acid (eq. 11.32).



(11.32)

17 g (0.1 mol)	0.1 g 7:3 Rh–Pt oxide 0.05 ml AcOH 35–40°C, 7.8–9.8 MPa H_2, 0.9 h	87% (90% by GC)
10 g (0.06 mol)	0.05 g Rh hydroxide 0.05 ml AcOH 85°C, 7.8–9.8 MPa H_2, 0.2 h	86.5% by GC

Rylander and Kilroy studied the formation of cyclohexyl phenyl ether intermediate in the hydrogenation of phenyl ether over binary platinum–rhodium oxide catalysts in cyclohexane at room temperature and atmospheric hydrogen pressure. The yield of the intermediate varied greatly with the catalyst composition. The highest yield (48%) was obtained over the catalyst consisting of 30% Pt–70% Rh.[149]

In order to study the hydrogenolysis in phenyl ether and its relationship to the formation of intermediates, Fukuchi and Nishimura hydrogenated phenyl ether and related compounds over unsupported ruthenium, rhodium, osmium, iridium, and platinum metals in *t*-butyl alcohol at 50°C and the atmospheric hydrogen pressure.[151] The results are shown in Tables 11.11 and 11.12. In general, the greater part of the initial products as determined by an extrapolation method has been found to be cyclohexyl phenyl ether, phenol, and cyclohexane (Table 11.11). Over ruthenium, however, cyclohexanol was found in a greater amount than phenol even in the initial products. Small amounts of cyclohexyl ether, 1-cyclohexenyl cyclohexyl ether, cyclohexanol, cyclohexanone, and benzene were also formed simultaneously.

The selectivity to cyclohexyl phenyl ether as a desorbed intermediate has also been determined by application of the equation in Scheme 11.7. In general, the selectivities obtained by both methods were in good accord. It is seen from the results that the selectivity to cyclohexyl phenyl ether decreases in the order Os > Rh > Ir > Pt > Ru. The yields of the ether at the maximum, however, are considerably lower than the corresponding selectivities with all the metals. The highest yield was obtained over rhodium (38.3%) rather than over osmium (29.0%), the metal of the highest selectivity for cyclohexyl phenyl ether, as the value of *K* was smaller over rhodium (0.37) than

TABLE 11.11 Hydrogenation of Phenyl Ether over Platinum Metals: Selectivities for Formation of Products at Initial Stage[a,b]

Catalyst	Cyclohexane + Benzene[c]	Cyclohexanone	Cyclohexanol	Phenol	Cyclohexyl Ether	1-Cyclohexenyl Cyclohexyl Ether	Cyclohexyl Phenyl Ether[d]
Ru	55.5	3.0	31.4	21.1	4.8	1.0	39.6 (40.5)
Rh	25.2	6.0	3.0	16.0	5.6	1.8	67.2 (68.7)
Os	26.8	0.0	7.2	19.6	2.2	0.0	70.1 (69.9)
Ir	46.2	5.2	3.6	37.4	2.2	0.0	51.5 (53.1)
Pt	50.3	5.7	2.2	42.4	2.6	0.0	47.5 (50.4)

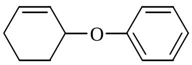
[a]Nishimura, S.; Fukuchi, E.; Fukui, S. Unpublished results; Fukuchi, E. Master's thesis, Tokyo Univ. Agric. Technol. (1992).
[b]Phenyl ether (0.1 ml) was hydrogenated over 0.007–0.015 g of metal black in 1.5 ml *t*-BuOH at 50°C and atmospheric pressure. Unless otherwise indicated, the selectivity to each product was obtained by an extrapolation method and is expressed in mol%, based on the number of moles of phenyl ether converted.
[c]The proportions of benzene were usually small and in the range of 0–30%. The amounts of these volatile products determined do not appear to be accurate, and the selectivities for these products were assumed to be equal to mol(cyclohexanone + cyclohexanol + phenol).
[d]The figures in parentheses are the selectivities determined by application of the equation in Scheme 11.7. The relative reactivity of cyclohexyl phenyl ether to phenyl ether (*K*) was 0.399 for Ru, 0.370 for Rh, 0.780 for Os, 1.61 for Ir, and 1.66 for Pt.

TABLE 11.12 Proportions of Hydrogenolysis (%) in Hydrogenation of Phenyl Ether, Cyclohexyl Phenyl Ether, and Phenol over Platinum Metals[a,b]

	Compound Hydrogenated		
Catalyst	Phenyl Ether[c]	Cyclohexyl Phenyl Ether	Phenol
Ru	55.5	3.2	2.3
Rh	25.2	0.9	4.4
Os	26.8	12.4	19.3
Ir	46.2	22.6	23.4
Pt	50.3	25.7	25.2

[a]Nishimura, S.; Fukuchi, E.; Fukui, S. Unpublished results; Fukuchi, E. Master's thesis, Tokyo Univ. Agric. Technol. (1992).
[b]The reaction conditions were the same with those in Table 11.11 except that 0.03 ml of the substrate was hydrogenated in the case of phenol.
[c]The proportion of hydrogenolysis at the initial stage of hydrogenation.

over osmium (0.78). It is noted that the selectivity to the intermediate ether is the lowest over ruthenium, reflecting the fact that the hydrogenolysis of the ether linkage at diphenyl ether occurs most extensively over ruthenium. This result with ruthenium is in sharp contrast to the case with alkyl phenyl ethers where ruthenium is usually among the metals of the least tendency toward hydrogenolysis,[146] as also seen from the results on the hydrogenation of cyclohexyl phenyl ether shown in Table 11.12, which also includes the results for phenyl ether and phenol for comparison. The proportion of hydrogenolysis in the hydrogenation of cyclohexyl phenyl ether was thus only 3.2% over ruthenium. The formation of neither of probable cyclohexenyl ether intermediates **4** or **5** can explain the extensive hydrogenolysis of phenyl ether over ruthenium, since the amounts of hydrogenolysis of **4** and **5** over ruthenium under the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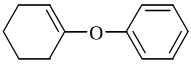
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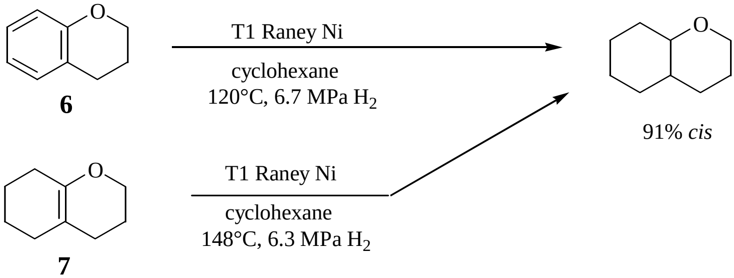
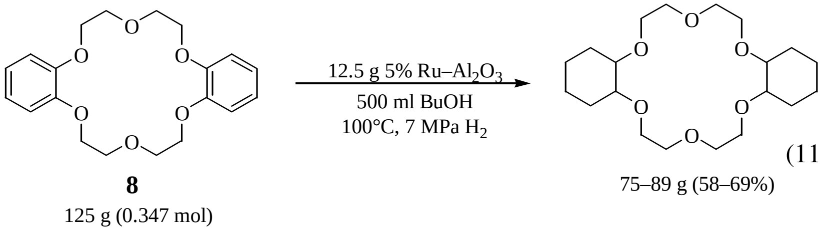
same conditions were found to be only 6.4 and 6.3%, respectively. It is also noted that, in contrast to an alkyl enol ether, an aryl enol ether **5** was not hydrogenolyzed to detectable extents over the third-row metals. On the other hand, an allyl aryl ether **4** may be one of the intermediates contributing to hydrogenolysis over the third-row metals, since **4** was hydrogenolyzed to the extents of 16–32% over these metals. The results in Table 11.12 also indicate that the hydrogenolysis of cyclohexyl phenyl ether and phenol is more extensive over osmium, iridium, and platinum (the third-row metals) than over ruthenium and rhodium (the second-row metals).

Griffiths and Wilcox obtained largely the *cis* isomer of octahydro-1-benzopyran (91%) in the hydrogenation of 3,4-dihydro-2*H*-1-benzopyran (**6**) over T1 Raney Ni in cyclohexane at 120°C and 6.7 MPa H_2.[152] The predominant formation of the *cis* isomer with **6** suggested that the hydrogenation might proceed via the enol ether **7**. This view has been supported by the observation that the hydrogenation of the enol ether **7** gave the same proportion of *cis*-octahydro-2*H*-1-benzopyran (eq. 11.33).



(11.33)

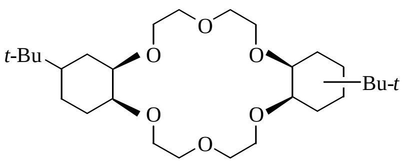
Pedersen prepared a number of cyclic polyethers by hydrogenation of the corresponding benzopolyethers over ruthenium dioxide or Ru–Al_2O_3 mostly in dioxane.[153] Dibenzo-18-crown-6 polyether (**8**) was hydrogenated to the corresponding cyclohexanoid derivative over 5% Ru–Al_2O_3 in 1-butanol at 100°C and ~7 MPa H_2 (eq. 11.34). Unexpectedly, Nishimura and Morimoto experienced that the same hydrogenation was unsuccessful over a commercial 5% Ru–Al_2O_3 and also over ruthenium hydroxide.[154] However, the hydrogenation could be readily completed over well-washed ruthenium black. Probably, trace amounts of alkaline substances contaminated in the catalysts prevented the hydrogenation to be completed, although usual phenyl ethers are hydrogenated without difficulty over these catalysts.



(11.34)

One patent describes a process for the preparation of *cis–syn–cis* isomer of [4,4′(5′)-di-*t*-butyldicyclohexano]-18-crown-6 (**9**) by hydrogenation of the corresponding dibenzo derivative over 5% Rh–Al_2O_3 in butanol in the presence of acetic acid at about 35–120°C and 1.4–6.9 MPa H_2.[155] The distribution ratio of the product for extraction of Sr^{2+} from aqueous HNO_3 was 4.1–4.2, which indicated that the product contained approximately 70% *cis–syn–cis* isomer.

Landre et al. report that hydrogenation of **8** over colloidal rhodium in the presence of phase transfer agents like tertiary amines and ammonium salts at 5 MPa H_2 affords the product with *cis–syn–cis/cis–anti–cis* isomer ratio of 95/5.[156] Mono- and dibenzo



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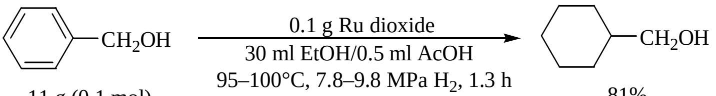
crown ethers have also been hydrogenated over Pd–C as catalyst to give the corresponding cyclohexanoid ethers in high yields.[157,158]

11.3 AROMATIC COMPOUNDS CONTAINING BENZYL–OXYGEN LINKAGES

Aromatic compounds with a benzyl–oxygen linkage, such as benzyl alcohols, and their ethers and esters, are known to be very labile to hydrogenolysis, when subjected to hydrogenation to saturate the aromatic ring. In general, benzyl esters are more readily hydrogenolyzed than benzyl alcohols and ethers; rather, the hydrogenolysis products are often formed predominantly. Aryl ketones are also susceptible to hydrogenolysis, since these ketones are usually first hydrogenated to benzyl-type alcohols. The hydrogenolysis of these benzyl–oxygen compounds is promoted markedly by acid, even in a trace amount.

Adkins and Covert hydrogenated benzyl alcohol using Ni–kieselguhr catalysts prepared by various procedures, but the best yield of cyclohexanemethanol was only 34%.[85] It appears that the hydrogenation over Raney Ni results in lower yields of cyclohexanemethanol (usually <20%).[159] The hydrogenation over an active platinized Raney Ni also gave only a 20% yield.[160]

However, ruthenium, rhodium, and rhodium–platinum catalysts have been found to be highly effective for the selective hydrogenation of these benzyl–oxygen compounds without loss of the oxygen functions. Thus, benzyl alcohol is hydrogenated to cyclohexanemethanol in high yield over ruthenium dioxide with addition of a small amount of acetic acid (eq. 11.35).[114]

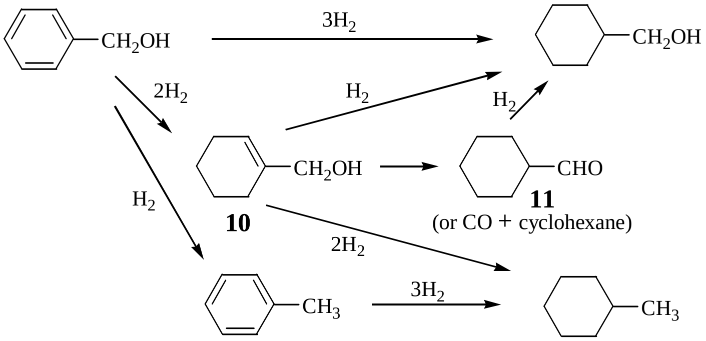


(11.35)

11 g (0.1 mol) 81%

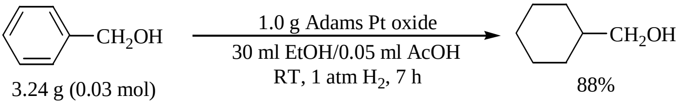
The same hydrogenation, however, was unsuccessful with rhodium–platinum[161] or rhodium[162] as catalyst because of a marked decrease in the rate during hydrogenation. This decrease in the rate is probably due to the poisoning of the catalysts by cyclohexanecarboxaldehyde (**11**) (or CO derived from it), which may be formed by isomerization of 1-cyclohexenemethanol (**10**) formed on the catalyst surface (Scheme 11.9).[163]

The formation of both **10** and **11** was observed in the reaction mixture from hydrogenation of benzyl alcohol, although only in small amounts. However, it has been shown that the addition of **10** or **11** strongly inhibits the hydrogenation of benzyl alcohol over rhodium and 7:3 rhodium–platinum catalysts. The hydrogenation of benzyl alcohol over platinum was inhibited to a lesser extent, and the formation of **11** in the course of hydrogenation was much less than that observed over rhodium because of a lower tendency of platinum toward the isomerization of **10** to **11**. Successful hydrogenation of benzyl alcohol over ruthenium as shown in eq. 11.35 is probably due to the circumstance that ruthenium catalysts can hydrogenate an aliphatic aldehyde to the corresponding alcohol with a considerable rate.[164]



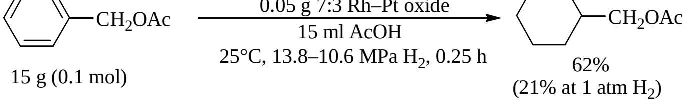
Scheme 11.9 Hydrogenation and hydrogenolysis pathways of benzyl alcohol and the formation of cyclohexanecarboxaldehyde.

Platinum catalysts, which usually tend to cause extensive hydrogenolysis, may be used for the selective hydrogenation of benzyl-type alcohols in the presence of a proper base. For example, benzyl alcohol can be hydrogenated to cyclohexanemethanol almost quantitatively over Adams platinum oxide in ethanol with addition of a small amount of acetic acid (eq. 11.36).[160]



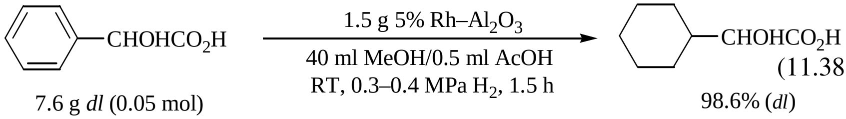
(11.36)

In this case, the alkaline substances contained in Adams platinum oxide probably worked to depress the hydrogenolysis effectively in collaboration with the added acetic acid. Without the addition of acetic acid, benzyl alcohol is not hydrogenated at all. Benzyl alcohol is largely hydrogenolyzed to give methylcyclohexane over Adams platinum in acetic acid or over reduced and washed Adams platinum in ethanol. Ichinohe and Ito found that the hydrogenolysis over Adams platinum decreased with respect to alcoholic solvents in the following order: primary > secondary > tertiary.[165] The amount of hydrogenolysis in the hydrogenation of benzyl–oxygen compounds may be decreased by application of a high hydrogen pressure. As an example, benzyl acetate, which is far more susceptible to hydrogenolysis than benzyl alcohol, gave cyclohexylmethyl acetate in 62% yield in the hydrogenation over 7:3 rhodium-platinum oxide in acetic acid at 25°C and 13–10.6 MPa H_2, compared to only 21% yield at an atmospheric pressure (eq. 11.37).[166] Over ruthenium dioxide cyclohexylmethyl acetate could be obtained in only 30% yield in the hydrogenation at 95–100°C and 7.8–9.8 MPa H_2 with addition of a small amount of acetic acid.[114]



(11.37)

In contrast to benzyl alcohol, α-substituted benzyl alcohols, benzyl ethers, and aryl ketones may be successfully hydrogenated over rhodium and rhodium–platinum catalysts to give the corresponding saturated products in high yields, as shown in eqs. 11.38–11.41. In the hydrogenations shown in eqs. 11.38 and 11.39, no racemization took place; D-mandelic acid afforded D-hexahydromandelic acid in 94% yield and *meso*- and *dl*-2,3-dicyclohexyl-2,3-butanediol were obtained in 93 and 94% yields, respectively, by hydrogenation of the corresponding diphenyl compounds.



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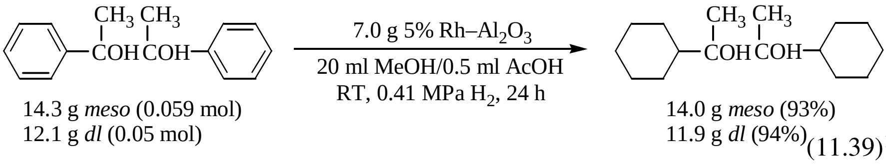

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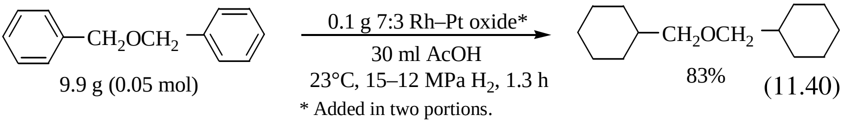

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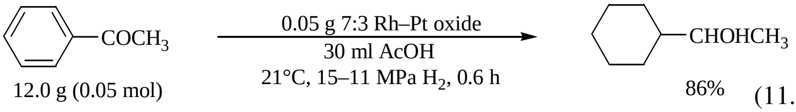
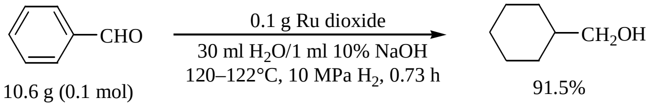
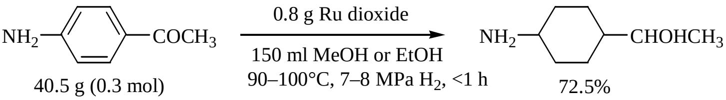


(11.41)[166]

Ruthenium catalysts are also effective for the selective hydrogenation of these easily hydrogenolyzable compounds at elevated temperatures and pressures. Besides an example shown in eq. 11.35, ruthenium dioxide has frequently been used for this type of hydrogenation. Cyclohexyl-α,ω-glycols were obtained in high yield by hydrogenation of the corresponding phenylglycols in ethanol at 80–120°C and 6.9–13.8 MPa H_2.[168] Benzaldehyde (eq. 11.42),[114,169] *l*-ephedrine (see eq. 11.58),[170] and *p*-aminoacetophenone (eq. 11.43)[171] were also hydrogenated successfully to the corresponding saturated alcohols in high yields over ruthenium dioxide as catalyst. Hydrogenation of acetophenone over osmium and platinum catalysts was found to



(11.42)

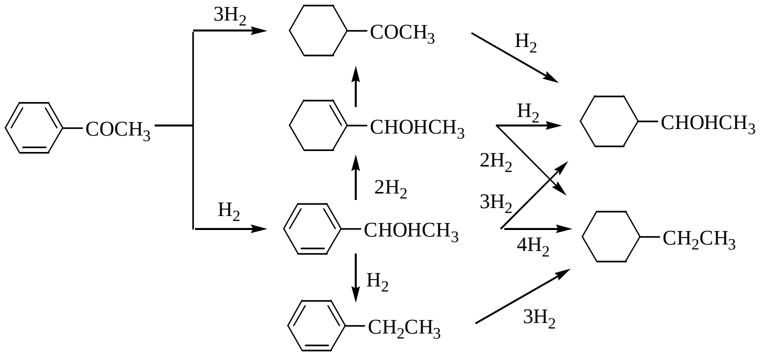


(11.43)

proceed partly via cyclohexyl methyl ketone simultaneously formed along with 1-phenylethanol.[172,173] Over ruthenium and rhodium catalysts, considerable portions of acetophenone have been found to proceed via cyclohexyl methyl ketone.[174,175] Taya et al. found that the saturated ketone was accumulated in an amount of as much as 50% at the maximum in the course of the hydrogenation of acetophenone without solvent over ruthenium hydroxide at 100°C and 7.8–9.8 MPa H_2.[175] The amount of hydrogenolysis product was only 2%. Over rhodium hydroxide the maximum yield of the ketone was smaller (21%) and the greater part of acetophenone was hydrogenated via 1-phenylethanol through which considerable amounts of hydrogenolysis products (ethylbenzene and ethylcyclohexane) were formed along with 1-cyclohexylethanol. Small amounts of cyclohexyl methyl ketone also appeared to be formed through isomerization of 1-(1-cyclohexenyl)ethanol over both ruthenium and rhodium catalysts. The hydrogenation and hydrogenolysis pathways of acetophenone are summarized in Scheme 11.10.

Rylander and Hasbrouck hydrogenated acetophenone over supported rhodium catalysts at room temperature and atmospheric pressure. In general, higher maximum yields of cyclohexyl methyl ketone and 1-cyclohexylethanol were obtained over 5% Rh–Al_2O_3 than over 5% Rh–C. The highest yield of the saturated ketone (41%) and 1-cyclohexylethanol (99%+) were obtained over 5% Rh–Al_2O_3 in *t*-butyl alcohol.[174]

Nishimura and Kasai studied the hydrogenation of acetophenone in *t*-butyl alcohol using carefully prepared ruthenium and rhodium blacks.[176] The selectivities for the formation of cyclohexyl methyl ketone and 1-phenylethanol as simultaneous products have been determined by application of the equation in Scheme 11.7. The values of K and f as well as the composition of the final products obtained are summarized in Table 11.13. Three ruthenium blacks—Ru (A), Ru (N), and Ru (B)—were prepared from the ruthenium hydroxide precipitated at pH 5, 7, and 7.8, respectively, by adding lithium hydroxide solution to an aqueous solution of ruthenium chloride. It is seen that the selectivity for the saturated ketone (see figures in parentheses) was considerably higher over Ru (B) (43%) than over Ru (A) (25%) and Ru (N) (20%). The selectivity over Ru (N) increased markedly to 65% at 100°C and 5.9–7.8 MPa H_2. Over rhodium



Scheme 11.10 Hydrogenation and hydrogenolysis pathways of acetophenone.

TABLE 11.13 Hydrogenation of Acetophenone over Ruthenium and Rhodium Catalysts[a,b]

			1-Phenylethanol			Cyclohexyl Methyl Ketone			% Product at Complete Hydrogenation	
Catalyst	Reaction T (°C)	H_2 P (MPa)	f	K	Yield at Maximum (%)[c]	f	K	Yield at Maximum (%)[c]	Ethyl-cyclo-hexane	1-Cyclo-hexylethanol
Ru (A)[d]	26	0.1	0.75	0.20	50.1	0.25	0.06	20.9	—[e]	—[e]
Ru (N)[d]	26	0.1	0.65	0.45	33.8	0.20	0.05	17.1	10.8	89.2
Ru (B)[d]	26	0.1	0.57	0.30	34.2	0.43	0.30	25.7	0.5	99.5
Ru (N)	100	5.9–7.8	—[f]	—[f]	—[f]	0.65	0.60	30.0	9.3	90.7
Rh	26	0.1	0.66	0.01	63.0	0.24	0.08	19.3	6.1	93.9
Rh[g]	26	0.1	0.70	0.05	59.8	0.30	0.05	25.6	0.2	99.8
Rh[h]	26	0.1	0.55	0.10	42.6	0.40	0.50	20.0	0.7	99.3
Rh	100	5.9–7.8	0.52	1.10	18.2	0.12	0.10	9.3	25.5[i]	68.4[i]

[a]Nishimura, S.; Kasai, T. Unpublished results; Kasai, T. Bachelor's thesis, Tokyo Univ. Agric. Technol. (1987).

[b]In the runs at 0.1 MPa H_2, 0.05 ml of acetophenone was hydrogenated over 0.005 g of Ru or Rh black in 1 ml of *t*-BuOH. At high pressure runs 1 ml of acetophenone was hydrogenated over 0.005 g of Ru or Rh black in 20 ml of *t*-BuOH. The Ru and Rh blacks were prepared by reduction with hydrogen of the corresponding hydroxide in water followed by washings with water. The reduction and washing process was repeated 2–3 times, until the water used as the reduction medium became practically neutral.

[c]Calculated maximum yields obtained by application of the equation in Scheme 11.7.

[d]Ru (A), Ru (N), and Ru (B) are the Ru blacks prepared from the Ru hydroxides precipitated at pH 5, 7, and 7.8, respectively.

[e]At 98.8% conversion of acetophenone, the composition of the product was 34.8% phenylethanol, 0.32% ethylbenzene, 1.95% ethylcyclohexane, 13.8% cyclohexyl methyl ketone, and 47.9% 1-cyclohexylethanol.

[f]The amounts of 1-phenylethanol detected were very small due to an extensive formation of cyclohexylethanol even at initial stages of hydrogenation, and the values could not be evaluated.

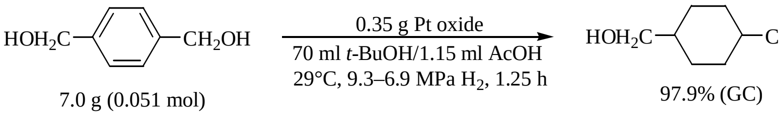
[g]LiOAc (0.2 mg) was added.

[h]$LiOH \cdot H_2O$ (1 mg) was added.

[i]The other product was cyclohexyl methyl ketone unhydrogenated (6.1%).

the selectivity for the saturated ketone became higher in the presence of lithium acetate (30%) or lithium hydroxide (40%), compared to that in the absence of base (24%). However, in contrast to ruthenium, the selectivity decreased to 12% at 100°C and 5.9–7.8 MPa H_2 over rhodium. It is also noteworthy that both the value of K for 1-phenylethanol and the amount of hydrogenolysis increased greatly under these conditions. Hydrogenolysis was almost completely depressed over Ru (B) (0.5%) and also over rhodium in the presence of lithium acetate (0.2%) or lithium hydroxide (0.7%). These results suggested that Ru (B), prepared from the ruthenium hydroxide precipitated at an alkaline medium, contained a trace amount of an alkaline substance, even after the hydroxide had been reduced to ruthenium metal with hydrogen in water followed by thorough washings with water, repeatedly until the water used for the reduction became neutral. The results in Table 11.13 clearly indicate that the hydrogenation pathway of acetophenone to cyclohexyl methyl ketone increases in the presence of alkali and at the same time the hydrogenolysis to give ethylcyclohexane is almost completely depressed over both ruthenium and rhodium.

The hydrogenation of 1,4-bis(hydroxymethyl)benzene (**12**) is an example that may be accompanied by rather extensive hydrogenolysis, resulting in decreased yield of the saturated glycol **13** (Scheme 11.11). This comes from the circumstances that the aromatic glycol **12** has two readily hydrogenolyzable benzyl–oxygen linkages; moreover, the rate of hydrogenation of the benzene ring would be much lower for **12** than for benzyl alcohol. This hydrogenation has been interested because the saturated glycol may be useful as a glycol component for polyesters, polyurethanes, and polycarbonates. Ichinohe and Ito obtained the saturated glycol **13** in high yields by hydrogenation of **12** over Adams platinum oxide in *t*-butyl alcohol containing a small amount of acetic acid at room temperature and high hydrogen pressures (eq. 11.44).[165] The amount of hydrogenolysis decreased with respect to the solvent in the order: primary > secondary > tertiary alcohol.



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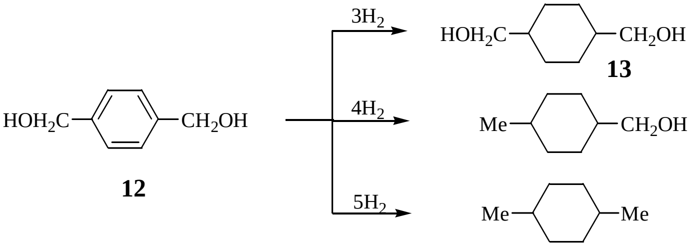


Scheme 11.11 Products of the hydrogenation of 1,4-bis(hydroxymethyl)benzene.

Since ruthenium is an effective catalyst for the hydrogenation of benzyl alcohol to cyclohexanemethanol (see eq. 11.35), a high yield of **13** is expected to be obtained by hydrogenation of **12** over ruthenium as catalyst. However, as described above in the hydrogenation of acetophenone, the amount of hydrogenolysis over ruthenium catalyst has been found to be sensitive to a trace amount of an alkaline substance. Nishimura et al., therefore, examined the effects of various alkaline substances on the extent of hydrogenolysis of **12**, using a ruthenium black that was unlikely to contain any alkaline substance.[177] The results are summarized in Table 11.14. As shown in the table, the ruthenium blacks, which were prepared by reduction of the ruthenium hydroxides that had been precipitated with an aqueous lithium hydroxide at pH > 6.0, were found to contain more than 200 ppm of lithium, even after repeated reductions with hydrogen in water and washings with water. The lithium appears to remain in the catalysts presumably in an insufficiently reduced part. It is seen that only small amounts of hydrogenolysis observed over these ruthenium blacks are associated with the lithium remaining in the catalysts. On the other hand, the ruthenium blacks from the ruthenium hydroxides precipitated at pH < 5.0 contain less than 10 ppm lithium

TABLE 11.14 Amounts of Hydrogenolysis in the Hydrogenation of 1,4-Bis(hydroxymethyl)benzene over Ru Blacks from Various Ru Hydroxides; Effects of Added Alkalies[a,b]

pH for Precipitation of Ru Hydroxide[c]	Li Content (ppm) of Ru Black[d]	Additive (mmol)	Hydrogenolysis (%)[e]
4.5	< 10	—	68.4
5.0	< 10	—	65.7
6.0	215	—	4.8
7.0	390	—	2.4
7.6	390	—	2.0
4.5	< 10	Na_2CO_3 (0.1)	17.2[f]
4.5	< 10	KOAc (0.1)	14.0[g]
4.5	< 10	NaOAc (0.4)	24.2
4.5	< 10	LiOAc (0.4)	1.6
4.5	< 10	NaO_2CCF_3 (0.4)	4.7
4.5	< 10	LiO_2CCF_3 (0.4)	5.4

[a]Nishimura, S.; Hirabayashi, M.; Okamoto, J.; Washizuka, J. Unpublished results; Nishimura, S.; Higashijima, M. *Hyomen* **1992**, *30*, 645. Reprinted with permission from Hyomen Danwakai & Colloid Konwakai, Japan.

[b]1,4-Bis(hydroxymethyl)benzene (0.5 g, 3.6 mmol) was hydrogenated over 0.02 g of Ru black in 10 ml THF at 80°C and 8 MPa H_2 for 3 h. The Ru blacks were prepared by reduction of Ru hydroxides with hydrogen in water followed by thorough washings with water to eliminate acidic or alkaline substances.

[c]The pH of the supernatant aqueous layer after Ru hydroxide had been precipitated from an aqueous solution of Ru chloride with Li hydroxide.

[d]The amount of Li extracted from Ru black with 5% hydrochloric acid solution 2 times at 45°C for 2 h.

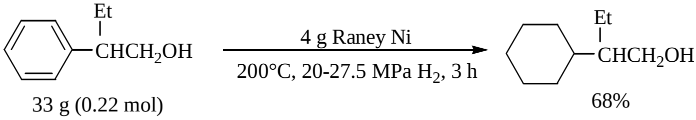
[e]Given by 100 × mol (1,4-dimethylcyclohexane + 4-methylcyclohexanemethanol × $\frac{1}{2}$)/mol 1,4-bis(hydroxymethyl)benzene converted. Unless otherwise noted, the product was analyzed at complete hydrogenation.

[f]7.2% conversion.

[g]23.8% conversion.

and cause extensive hydrogenolysis. The effects of the addition of various alkaline substances have been examined using a ruthenium black containing less than 10 ppm lithium. Of the alkaline substances investigated, LiOAc was found to be the most effective for depressing the hydrogenolysis. NaO_2CCF_3 or LiO_2CCF_3 appears to be less effective than LiOAc, probably because these bases are too weak to depress the hydrogenolysis effectively. It is to be noted that the hydrogenolysis was more extensive with addition of NaOAc than with LiOAc and that the addition of stronger bases KOAc and Na_2CO_3 seriously inhibited the hydrogenation.

The 2- and 3-phenyl-substituted alcohols and their ethers show much lower tendencies toward hydrogenolysis than do benzyl-type alcohols and their ethers, and may give high yields of the corresponding saturated compounds even in hydrogenation over nickel catalysts, as seen in the following examples:[178]



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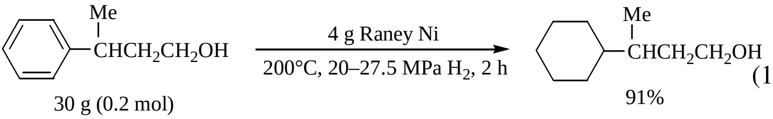
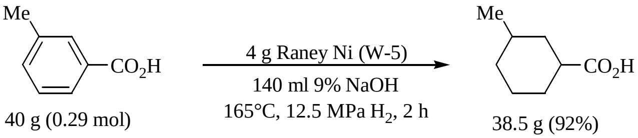


(11.46)

11.4 CARBOXYLIC ACIDS AND ESTERS

Over nickel catalysts, aromatic carboxylic acids can be hydrogenated without difficulty as their sodium salts. Thus, *o*-[179] and *m*-toluic acids,[180] *m*-hydroxybenzoic acid,[181] and tetrephthalic acid[182] were hydrogenated to the corresponding saturated acids in high yields over Raney Ni at elevated temperatures and pressures. Examples are shown in eqs. 11.47 and 11.48. *o*-Toluic acid and terephthalic acid afforded the *trans* acids predominantly under these conditions.



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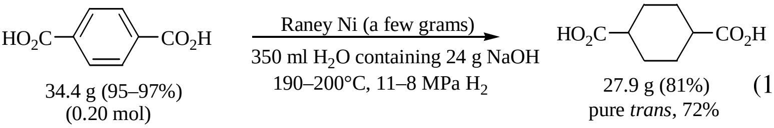
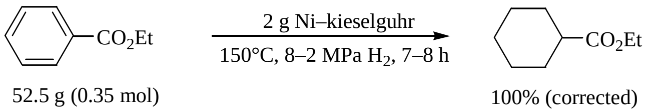


(11.48)

Aromatic esters are hydrogenated without solvent or in alcohol. Ethyl benzoate (eq. 11.49),[11] ethyl phenylacetate,[183] methyl salicylate (eq. 11.50),[86a] and diethyl phthalate (eq. 11.51)[183] were hydrogenated almost quantitatively to the corresponding cyclohexane derivatives over Ni–kieselguhr at 150–200°C. The hydrogenation of the ethyl

esters of *o*-, *m*-, and *p*-hydroxybenzoic acids over Raney Ni in ethanol was successful in the presence of 0.3 mol% (on the basis of phenolic ester) of sodium ethoxide at 160–220°C and 24–27 MPa H_2 (see eq. 11.14).[79]



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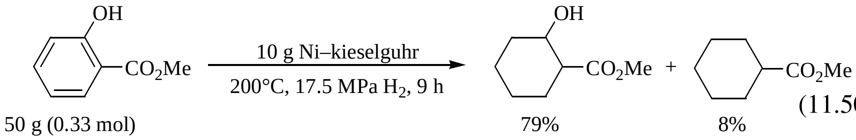

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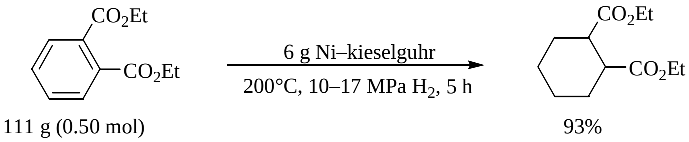
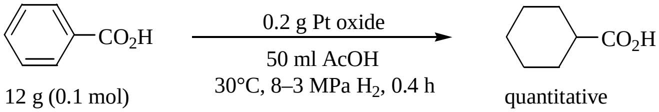


(11.51)

Over platinum, rhodium–platinum, and rhodium catalysts, aromatic carboxylic acids and their esters may be hydrogenated at room temperature and a low hydrogen pressure.[6,7,20] Platinum and rhodium–platinum oxides prepared by the Adams procedure have been used usually in acetic acid as solvent, because the alkaline substances contained in these catalysts may prevent the hydrogenation of the aromatic ring.[19] For synthetic purposes, however, application of high hydrogen pressure has been shown to be effective for the hydrogenations using these catalysts.[23,24] The times for completing hydrogenations can be reduced markedly under high pressures. For example, benzoic acid and ethyl benzoate were rapidly hydrogenated to the corresponding cyclohexane derivatives over platinum oxide and 7:3 rhodium–platinum oxide, receptively, under high pressures (eqs. 11.52[184] and 11.53[24]).



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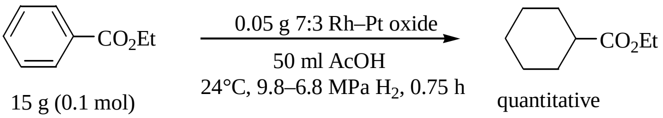


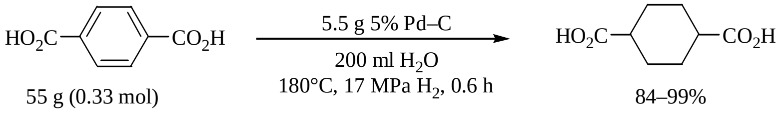
(11.53)

The benzoic acid prepared by an air oxidation of toluene contains small amounts of various compounds that decrease the catalytic activity of platinum metal catalysts. The benzoic acid purified by sublimation is hydrogenated much more rapidly than an unpurified one. On a large scale, however, treatment of commercial benzoic acid with Pd–C at 100–200°C under high hydrogen pressure in a solvent for hydrogenation or, better, treatment with 0.2–10% (for benzoic acid) of concentrated sulfuric acid at

140–210°C followed by neutralization and distillation, was claimed to be effective.[185,186] The benzoic acid thus purified was hydrogenated at the rate of 20.5 mol · h^{-1} · g $metal^{-1}$ over a 5% Rh–Pt–C catalyst (Rh : Pt = 2 : 1) in cyclohexanecarboxylic acid at 80°C and 4.9 MPa H_2, compared to the rate of 11.4 mol · h^{-1} · g $metal^{-1}$ with unpurified benzoic acid. With Rh–Pt–C catalysts (5 wt% metal) of various compositions, the maximum rate of 21 mol · h^{-1} · g $metal^{-1}$ was obtained at the composition of Rh:Pt = 2:1, compared to 12 and 5 mol · h^{-1} · g $metal^{-1}$ with the corresponding Rh–C and Pt–C catalysts, respectively.[187] Rylander et al. observed a pronounced promoting effect of water in the hydrogenation of benzoic acid over 5% Ru–C in cyclohexanecarboxylic acid at 130°C and 15.5 MPa H_2, and also over 5% Rh–C and 5% Pd–C although to lesser extents.[25] Pd–C has also been found to be a useful catalyst in an industrial process for the hydrogenation of benzoic acid to cyclohexanecarboxylic acid at elevated temperatures and pressures to give almost quantitative yields.[188] Cyclohexanecarboxylic acid was used as a solvent for this hydrogenation. Pd–C catalyst was also used in the hydrogenation of *p*-toluic acid to 4-methylcyclohexanecarboxylic acid in water at 170°C and 4.9–6.9 MPa H_2.[189]

Hydrogenation of dimethyl phthalate over platinum oxide in acetic acid at room temperature is noteworthy in that the *cis* isomer is formed exclusively.[190] On the other hand, hydrogenation of dimethyl terephthalate gives a mixture of the *cis* and *trans* saturated isomers, although the *cis* isomer is usually formed in excess (e.g., 71% *cis* over platinum and 83% *cis* over 7:3 rhodium–platinum in AcOH at 25°C and 1 atm H_2).[191] Hydrogenation of dimethyl terephthalate over Pd–C is claimed to be performed at significantly lower pressures in cooperation with other group VIII metals such as nickel, platinum, ruthenium, or a mixture thereof.[192] For example, dimethyl terephthalate was hydrogenated at 155–177°C and 12.5 MPa H_2 using 1% Pd–Al_2O_3 containing 0.1% nickel to give the reaction rates 24–45% greater than those for unpromoted Pd–Al_2O_3.

Terephthalic acid was hydrogenated over platinum oxide in acetic acid (70°C, 1 atm H_2) to give a mixture consisting of 75% *cis*- and 25% *trans*-cyclohexane-1,4-dicarboxylic acid.[182] Terephthalic acid was also hydrogenated over Pd–C or Ru–C. The hydrogenation over 5% Pd–C was performed in water at 180°C and 17 MPa H_2 to give high yields of cyclohexane-1,4-dicarboxylic acid (eq. 11.54).[193] Similar results were also obtained in the hydrogenation over Ru–C.

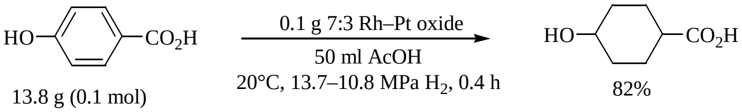


(11.54)

Commercial terephthalic acid may be purified by methods similar to those used for the purification of benzoic acid[185,186] by treating the acid with Pd–C and hydrogen, for example, at 290°C and 8.9 MPa H_2, in the presence of acid.[194]

Hydrogenation of *o*-, *m*- and *p*-hydroxybenzoic acids over platinum catalysts is labile to hydrogenolysis to give cyclohexanecarboxylic acid.[195] The proportion of hydrogenolysis increases in the order *ortho* < *meta* < *para*, and it amounted to as much

as 84.5% in the hydrogenation of the *para* isomer in water at 21–25°C and atmospheric pressure, compared to 20.8 and 67.8% for the *ortho* and *meta* isomers, respectively.[196] The proportion of hydrogenolysis is much smaller, and 4-hydroxycyclohexanecarboxylic acid is obtained in high yield in high-pressure hydrogenation over 7 : 3 rhodium–platinum oxide in acetic acid (eq. 11.55).[166] The yield decreased to 65% in the hydrogenation at 1 atm H_2.



(11.55)

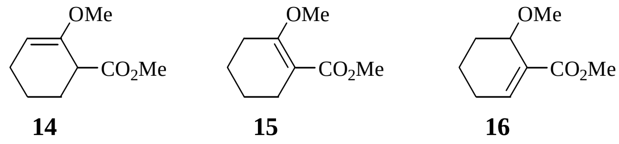
The ethyl ester of *p*-hydroxybenzoic acid was hydrogenated to give high yields of the saturated 4-hydroxy ester either over Pd–$SrCO_3$ in dioxane (see eq. 11.24)[113] or ethyl acetate[195] at 155–160°C, and over rhodium oxide at 50–65°C or over ruthenium oxide at 95–100°C in ethanol with small amounts of acetic acid (see eq. 11.25),[114] under high hydrogen pressures.

Kambara and Nishimura studied the hydrogenation of the methyl esters of *o*-, *m*-, and *p*-methoxybenzoic acid over platinum group metals in *t*-butyl alcohol at 60°C and atmospheric hydrogen pressure.[197] As seen from the results shown in Table 11.15, hydrogenolysis occurred most extensively over platinum and iridium and much less extensively over rhodium and ruthenium, especially with the *meta* and *para* isomers. It is noted that the *ortho* isomer was hydrogenolyzed as extensively as the *meta* isomer over platinum and iridium, and much more extensively than the *meta* and *para* isomers over rhodium and ruthenium. Over Pd–C the most extensively hydrogenolyzed was the *meta* isomer. One of the reasons for the extensive hydrogenolysis in the case of the *ortho* isomer can be attributed to the direct formation of methyl benzoate, which amounted to 17.1% over rhodium, 20.7% over ruthenium, and 16.6% over platinum,

TABLE 11.15 Proportions of Hydrogenolysis in Hydrogenation of Methyl Methoxybenzoates over Platinum Metals[a,b]

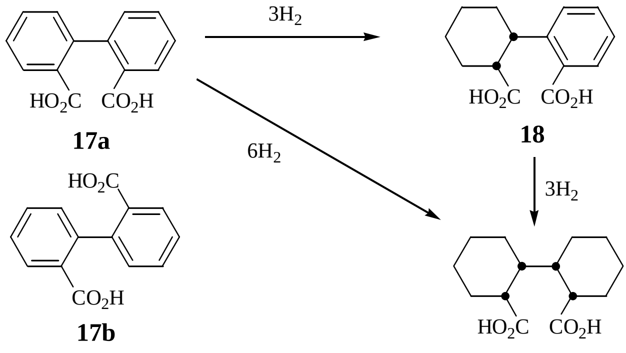
	Proportion of Hydrogenolysis (%)		
Catalyst	*Ortho*	*Meta*	*Para*
Rh	17.3	6.7	5.6
Ru	40.3	9.9	3.7
Pt	69.1	52.6	88.6
Ir[c]	43.6	58.7	67.9
Pd–C[d]	34.5	62.4	25.6

[a]Kambara, H.; Nishimura, S. Unpublished results; Kambara, H. Master's thesis, Tokyo Univ. Agric Technol. (1991).
[b]Methyl methoxybenzoate (50 μl) was hydrogenated over 5 mg catalyst in 2 ml *t*-BuOH at 60°C and 1 atm H_2.
[c]The values were obtained at 40% hydrogenation.
[d]The values were obtained at 70% hydrogenation.



as estimated by extrapolating the selectivity to the initiation. The amount of hydrogenolysis in the *ortho* isomer over rhodium (17.3%) can be accounted for mostly by this type of direct cleavage of the aryl–oxygen bond. On the other hand, the extensive hydrogenolysis over platinum (69.1%) may result mostly through the enol ether intermediates **14** and **15**, since these enol ethers were found to be hydrogenolyzed to the extents of 61 and 67%, respectively, over platinum under similar conditions. Since the enol ethers **14** and **15** were hydrogenolyzed only slightly over ruthenium (1.6 and 1.2%, respectively), the extensive hydrogenolysis (40.3%) of the *ortho* isomer over ruthenium cannot be explained by the formation of methyl benzoate alone, as in the case with rhodium. Since the third intermediate, probably of the structure **16**, was formed in a selectivity of 13.8% at the initial stage, it is suggested that this intermediate has contributed to the extensive hydrogenolysis over ruthenium, although this suggestion has not been confirmed experimentally. The extensive hydrogenolysis over Pd–C (34.5%) could be explained neither by the enol ether intermediates nor by the formation of methyl benzoate, since **14** and **15** were hydrogenolyzed only to the extents of 0.9 and 1.0%, respectively, and the formation of methyl benzoate was not observed at all over this metal.

2,2′-Diphenic acid (**17**) and its ester as well as *cis*-hexahydro-2,2′-diphenic acid (**18**) are all hydrogenated largely to give *cis–syn–cis*-perhydro derivatives over platinum oxide in acetic acid, in the same stereochemical manner as do its anhydride and the phenanthrene derivatives related to it (Scheme 11.12).[198,199] Linstead et al. explained the results on the assumption that the diphenic acid or its ester are hydrogenated in the coiled form (**17a**), rather than in the zigzag form (**17b**), which is expected to yield the product with a *cis–anti–cis* configuration.[62]

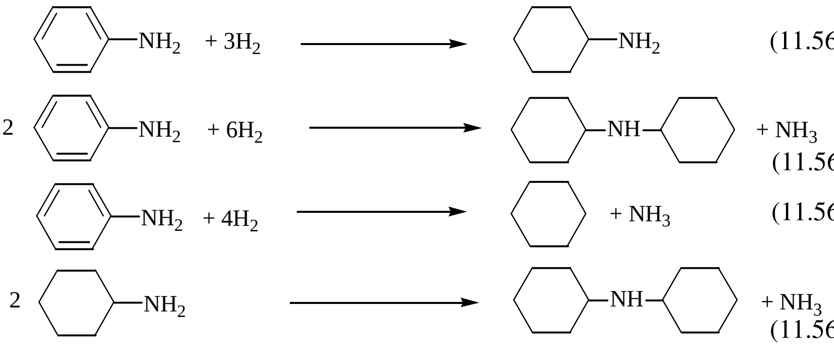


Scheme 11.12 Stereochemistry of hydrogenation of 2,2′–diphenic acid and *cis*-hexahydro-2,2′-diphenic acids.

11.5 ARYLAMINES

Hydrogenation of arylamines usually requires somewhat higher temperatures and/or longer reaction times than does hydrogenation for other aromatic compounds. The effect of hydrogen pressure is also greater for aniline than for benzene and phenol. The rate of hydrogenation of aniline over Ni–kieselguhr in methylcyclohexane at 170°C was 3–4 times greater at 19–34 MPa H_2 than that at 3.4 MPa H_2,[200] and application of hydrogen pressures of 20–30 MPa was recommended for the more inactive amines.[201] The rate of hydrogenation of aniline over 7:3 rhodium–platinum oxide in acetic acid at 27°C also greatly increased with increasing hydrogen pressure. The rate at 14.6 MPa H_2 was approximately 30 times as great as that at 1 atm H_2.[202]

An important side reaction in the hydrogenation of aniline is the formation of secondary amine (eq. 11.56b), which may accompany the formation of primary amine (eq. 11.56a). At high temperatures, in particular in the vapor phase, the cleavage of the amino group to give a hydrocarbon and ammonia (eq. 11.56c) as well as the formation of secondary amine from 2 mol of cyclohexylamine (eq. 11.56d) may occur. According to Winans, in liquid-phase hydrogenations over nickel and cobalt catalysts, the reaction of eq. 11.56c occurs at temperatures higher than 275°C and is not important below 325°C. The reaction of eq. 11.56d may occur at 200°C or higher, but the rate is seldom great.[203] Therefore, the reactions expressed by eqs. 11.56c and 11.56d are not important in normal hydrogenations under high pressures. In the hydrogenation of aniline over Raney Ni at 5 MPa H_2, the formation of cyclohexane by eq. 11.56c was less than 1% at 250°C, and the formation of dicyclohexylamine by eq. 11.56d did not take place below 220°C and began to occur only to a small extent at 220°C.[204]



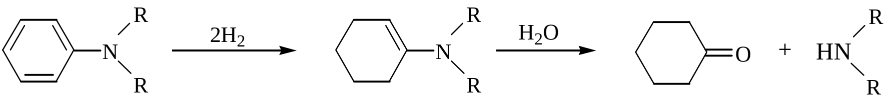
(11.56a)

(11.56b)

(11.56c)

(11.56d)

The presence of water may lead to the formation of cyclohexanone or cyclohexanol by the hydrolysis of the enamine or imine intermediate.[204,205] The hydrolysis takes place especially readily in the hydrogenation of *N*,*N*-dialkylanilines (eq. 11.57).

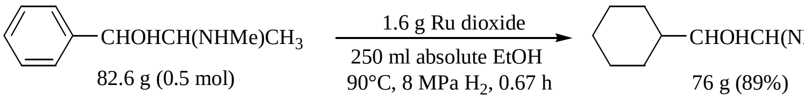


(11.57)

When anilines are hydrogenated over the catalysts such as nickel and cobalt, which usually require rather high temperatures, *N*-alkylation to give *N*-alkylcyclohexylamine may occur if alcohols are used as solvents.[206] Usually higher selectivities to cyclohexylamine are obtained over cobalt catalysts than over nickel catalysts, although higher reaction temperatures may be required for cobalt catalysts. An effective cobalt catalyst described by Winans for the hydrogenation of aniline contained the CaO freshly prepared by calcination of calcium hydroxide at 900°C and gave the product of a high primary to secondary amine ratio of 8.5, compared to 2.2–2.8 over the catalyst without CaO, at 285°C and a high hydrogen pressure.[203] Hydrogenation of aniline with addition of dicyclohexylamine was also reported to be effective to depress the formation of secondary amine.[203] The effect of added dicyclohexylamine is probably due to the reversibility of the reaction in eq. 11.55d to form 2 mol of cyclohexylamine at high temperatures (>200°C).[205] In one patent, aniline was hydrogenated to give the product consisting of 97.1% cyclohexylamine, 1.65% dicyclohexylamine, 0.5% aniline, and 0.4% benzene over a catalyst consisting of 40% Co_3O_4 and 60% CaO at 220°C and 8–10 MPa H_2. The Co_3O_4 was prepared by calcination of basic cobalt carbonate, obtained from cobalt nitrate, at 300–400°C.[207]

Ruthenium catalysts have been shown to be highly effective for the hydrogenation of aromatic amines.[170,171,208–210] Hydrogenation of anilines over ruthenium catalysts proceeds at lower temperatures than over nickel and cobalt catalysts and affords the corresponding cyclohexylamines in high yields. Freifelder and Stone hydrogenated various nuclear substituted anilines over ruthenium dioxide in methyl or ethyl alcohol at 90–100°C and 7–9 MPa H_2.[171] Under these conditions, most hydrogenations were completed within 2 h with use of 2 wt% of catalyst and gave high yields of the corresponding cyclohexylamines. *N*-Alkylation did not occur under these conditions. The effectiveness of ruthenium dioxide for the hydrogenation of anilines is probably associated with alkaline substances contained in the catalyst. The secondary amine was detected only in the hydrogenation of *p*-(2-pentyl)aniline, where it was the major product, and the primary amine was obtained in only 11.5% yield. In the hydrogenation of alkoxyanilines, the hydrogenolysis of alkoxy groups occurred extensively, resulting in lower yields of the corresponding alkoxycyclohexylamines, except with 2-butoxyaniline. The hydrogenolysis took place most extensively with methoxyanilines where the yields of the corresponding methoxycyclohexylamines were only 35–42.5%, while the hydrogenolysis was not significant with 2-butoxyaniline, where 2-butoxycyclohexylamine was obtained in 84.7% yield. Extensive hydrogenolysis also occurred in the hydrogenation of *p*-*N*,*N*-dialkylaminoanilines. For example, the hydrogenation of *N*,*N*-dimethyl-*p*-phenylenediamine gave 4-*N*,*N*-dimethylaminocyclohexylamine in only 20% yield. *p*-Aminoacetophenonone was hydrogenated to give a 72.5% yield of the corresponding saturated aminoalcohol. This hydrogenation was unsuccessful over platinum catalyst; only 4-ethylcyclohexylamine was obtained because of extensive hydrogenolysis.[211] 2-Phenylalkylamines were also hydrogenated over ruthenium dioxide to give excellent yields of ring-hydrogenated amines.[170] The difficulty in hydrogenation of these amines has been reported by other investigators.[212,213] An example of the use of ruthenium dioxide is given in eq. 11.58 for *l*-

ephedrine, which was hydrogenated to the corresponding cyclohexyl compound without hydrogenolysis of the OH group and without change in rotation.



(11.58)

Nishimura et al. studied the effects of added alkaline substances on rhodium- and ruthenium-catalyzed hydrogenation of aromatic amines.[214,215] In alcohol solvents the hydrogenation of aniline at 80°C and 7.8–4.4 MPa H_2 was strongly inhibited by the ammonia that was formed along with the formation of dicyclohexylamine, especially with rhodium catalyst. Dicyclohexylamine was found to inhibit the hydrogenation to a much lesser extent than ammonia. However, in the presence of small amounts of alkali, the hydrogenation was not inhibited even by the addition of ammonia, and, at the same time, the formation of dicyclohexylamine was depressed almost completely over both rhodium and ruthenium catalysts. Over ruthenium hydroxide, aniline was hydrogenated most rapidly when LiOH was added in amounts exceeding 30 mg (as monohydrate) to 65 mg of the catalyst at 110°C and 6.9–9.8 MPa H_2. The stronger alkalies NaOH and KOH greatly depressed the rate of hydrogenation even when added in amounts less than 10% of the weight of catalyst. The effects of added alkali and alkaline-earth metal hydroxides and sodium carbonate were compared in the hydrogenation of *o*-toluidine where differences in the effects of the bases were observed more clearly than in aniline (Table 11.16). It is seen that the hydrogenation proceeds most

TABLE 11.16 Effects of Added Alkalies on the Ruthenium-Catalyzed Hydrogenation of *o*-Toluidine[a,b]

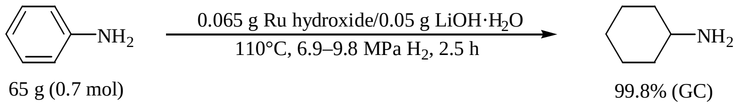
Catalyst	Amount (mg)	Additive	Amount (mg)	Reaction Time (h)	*o*-Toluidine Hydrogenated (%)	Secondary Amine Formed (%)[c]
Ru hydroxide	30	None	—	4[d]	79.4	6.7
Ru hydroxide	30	$LiOH \cdot H_2O$	30	6	99.8	0.7
Ru hydroxide	30	NaOH	1.5	6	85.1	2.3
Ru hydroxide	30	NaOH	3.0	6	55.0	—
Ru hydroxide	30	Na_2CO_3	100	6	94.4	1.9
Ru hydroxide	30	$Ca(OH)_2$	80	6	96.4	2.4
Ru hydroxide	30	$Ba(OH)_2 \cdot 8H_2O$	100	6	90.6	2.7
5% Ru–C	360	None	—	10.5	46.8	7.4
5% Ru–C	360	$LiOH \cdot H_2O$	120	10.5	99.7	0.3
5% Ru–C	360	$LiOH \cdot H_2O$	360	10.5	97.8	Trace

[a]Data of Nishimura, S.; Kono, Y.; Otsuki, Y.; Fukaya, Y. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 240. Reprinted with permission from Chemical Society of Japan.
[b]*o*-Toluidine (25 g, 0.23 mol) was hydrogenated at 110°C and 6.9–9.8 MPa H_2.
[c]Based on the hydrogenated products.
[d]The hydrogenation almost stopped.

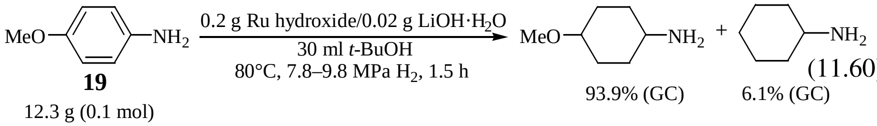
rapidly and the formation of secondary amine is depressed most effectively in the presence of LiOH among the various alkaline substances investigated. When other bases or no base were added, the formation of secondary amine increased and it was difficult to complete the hydrogenation within a reasonable time.[215,216]

The effects of solvents on the hydrogenolysis that accompanies the hydrogenation of *p*-anisidine (**19**, eq. 11.60), *N*,*N*-dimethyl-*p*-phenylenediamine (**20**, eq. 11.61), and 1,3-bis(aminomethyl)benzene (**21**, eq. 11.62) have been studied over ruthenium hydroxide in the presence of LiOH.[215,217] The results are summarized in Table 11.17. In general, the hydrogenolysis takes place most extensively in methanol and ethanol, and to lesser extents in higher primary alcohols as well as secondary and tertiary alcohols. Hydrogenations in ethers required longer reaction times than in alcohols and resulted in greater amounts of hydrogenolysis. The rates of hydrogenation and extents of hydrogenolysis in methylcyclohexane depended on the substrates. In the case of **20** the proportion of hydrogenolysis was the smallest in methylcyclohexane, in contrast to **19** and **21**. From these results it may be deduced that the proportion of hydrogenolysis increases with increasing polarity of solvents, as estimated by their dielectric constants, and also depends on the rates of hydrogenation; the greater rates are favorable for the depression of hydrogenolysis. The relationship is most clearly seen in the case of *p*-anisidine, where the effect of solvents on hydrogenolysis was the most pronounced.[217]

Examples of the hydrogenation of various aromatic amines in the presence of ruthenium hydroxide and LiOH are shown in eqs. 11.59–11.62. In most cases hydrogenations were completed within a few hours and high yields of the corresponding saturated primary amines were obtained under these conditions. It is seen that the yields of desired primary amines in hydrogenation of **19** and **20** (eqs. 11.60 and 11.61, respectively) are much greater than those reported by other investigators using ruthe-



(11.59)



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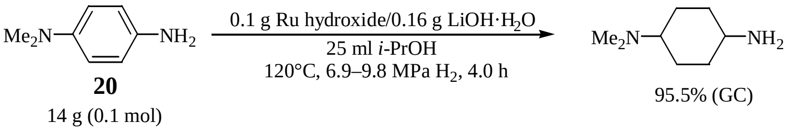
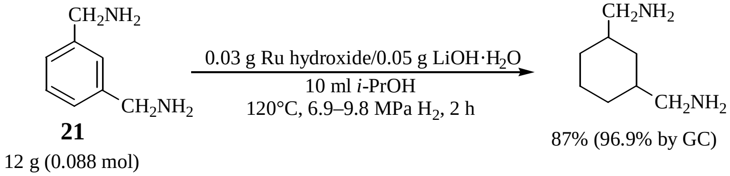
(11.60)



20

(11.61)



21

(11.62)

TABLE 11.17 Effects of Solvents on Hydrogenation–Hydrogenolysis of Aromatic Amines over Ruthenium Catalyst[a]

		p-Methoxyaniline[c]		*N,N*-Dimethyl-*p*-phenylenediamine[d]		1,3-Bis(aminomethyl)benzene[e]	
Solvent	ε at 80°C[b]	Reaction Time (h)	Hydrogenolysis (%)	Reaction Time (h)	Hydrogenolysis (%)	Reaction Time (h)	Hydrogenolysis (%)
MeOH	23.9	5.8	35.1	4.3	29.3	3.5	9.5
EtOH	16.8	2.5	30.1	3.3	35.8	4.6	8.8
PrOH	13.1	2.0	26.2	3.7	15.4	2.8	5.4
i-PrOH	12.2	2.3	16.5	2.7	13.4	2.4	5.1
BuOH	11.3	2.5	21.7	3.0	14.7	—	—
s-BuOH	9.4	3.0	13.1	2.7	13.3	2.1	5.6
t-BuOH	6.1	2.5	8.5	3.0	15.9	2.6	7.0
t-PeOH	—	—	—	—	—	2.4	4.4
THF	6.7	5.0	11.3	4.7	36.1	—	—
i-Pr_2O	3.3	6.5	15.6	4.3	18.3	6.2	11.7
Bu_2O	—	—	—	—	5.6	9.6	
C_7H_{14}[f]	1.9	5.5	13.1	3.3	10.1	3.0	5.7

[a] Data of Nishimura, S.; Yoshino, H. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 499; Nishimura, S.; Kono, Y.; Otsuki, Y.; Fukaya, Y. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 240. Reprinted with permission from Chemical Society of Japan.

[b] The dielectric constants of solvents at 80°C obtained by extrapolating the values taken from *Landolt-Börnstein Tabellen*, 6 Auf. II; Springer-Verlag, 1959; Teil 6, p 613.

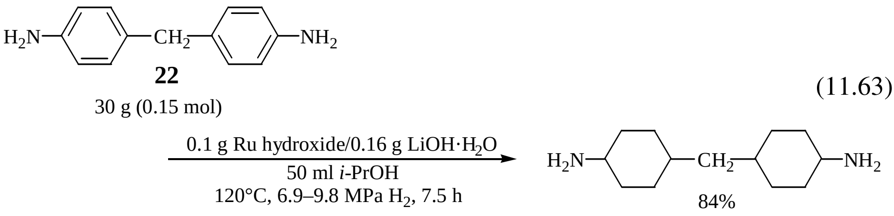
[c] *p*-Methoxyaniline (12.3 g, 0.1 mol) was hydrogenated in 30 ml of solvent at 80°C and 7.8–9.8 MPa H_2 in the presence of 0.1 g of Ru hydroxide and 0.01 g of $LiOH \cdot H_2O$.

[d] *N,N*-Dimethyl-*p*-phenylenediamine (4.1 g, 0.03 mol) was hydrogenated in 20 ml of solvent at 130°C and 6.9–9.8 MPa H_2 in the presence of 0.03 g of Ru hydroxide and 0.006 g of $LiOH \cdot H_2O$.

[e] 1,3-Bis(aminomethyl)benzene (4.1 g, 0.03 mol) was hydrogenated under the same conditions as for *N,N*-dimethyl-*p*-phenylenediamine but at 120°C.

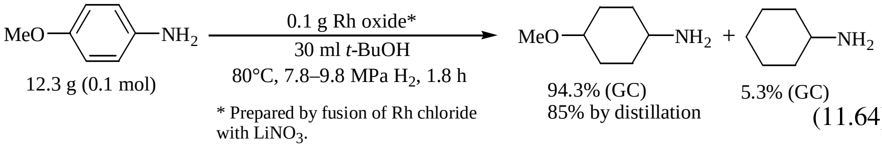
[f] Methylcyclohexane.

nium dioxide as catalyst.[171] Bis(4-aminophenyl)methane (**22**) is also hydrogenated without difficulty to give a high yield of the corresponding bis(aminocyclohexyl)methane with use of a much lesser amount of catalyst (0.3 wt%) (eq. 11.63) than in a similar hydrogenation using ruthenium dioxide (2 wt%).[209] In one patent, use of alkylamines or alkylenediamines as solvent is recommended for the hydrogenation of **21** over Ru–Al_2O_3.[218] For example, 1,3-bis(aminomethyl)cyclohexane was obtained in 95% yield in hydrogenation over Ru–Al_2O_3 in diethylamine.



(11.63)

Rhodium catalysts have also been employed for the hydrogenation of aromatic amines, especially under milder conditions than ruthenium. Freifelder et al. hydrogenated various alkoxyanilines over 5% Rh–Al_2O_3 in ethanol or in ethanol containing 1 equiv of acetic acid at 60°C and 0.35 MPa H_2.[219] The hydrogenolysis of alkoxyl groups was not extensive; it occurred at rates of 24.5% with *p*-anisidine and 14.4% with 4-butoxyaniline. However, small or significant amounts of alkoxyanilines (1.0–33.0%) remained unchanged after 4–31 h of reaction. These results appear to indicate that rhodium catalysts are more susceptible to the poisoning by nitrogen bases than are ruthenium catalysts. Since the decrease in rate and secondary amine formation in the hydrogenation of aromatic amines may be reduced in the presence of a small amount of alkali,[214] Nishimura et al. studied the hydrogenation of alkoxyanilines with alkali-promoted rhodium catalysts, and found that the rhodium oxide prepared by fusion of rhodium chloride with lithium nitrate afforded excellent yields of methoxy- and ethoxycyclohexylamines in the hydrogenation of the corresponding methoxy- and ethoxyanilines in *t*-BuOH at 80–90°C and 7.8–9.8 MPa H_2.[220] Generally, hydrogenolysis was at a low level (3.1–5.9%) and hydrogenations were completed within a few hours, using less than 2 wt% catalyst:substrate ratio. The results obtained with this rhodium oxide were more satisfactory than with a combination of rhodium hydroxide and LiOH, which had been shown to be an effective catalyst system for the hydrogenation of aniline.[214] An example of the use of this rhodium oxide is shown in eq. 11.64 for the hydrogenation of *p*-anisidine (see also eq. 11.60).

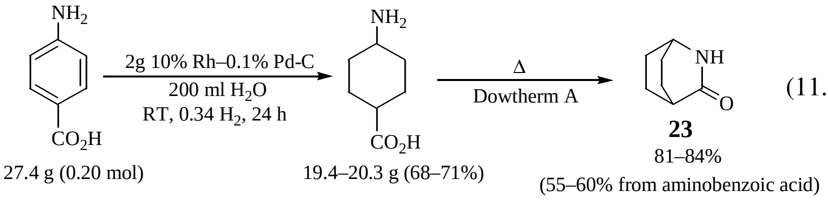


(11.64)

The same hydrogenation was often inhibited at a later stage of the reaction with the rhodium oxide prepared by conventional sodium nitrate fusion. Rh–Al_2O_3 was used

successfully in the hydrogenation of a mixture of 2,4- and 2,6-toluenediamine in *i*-PrOH-THF at 160°C and 8.6 MPa H_2 to give the corresponding methylcyclohexanediamine in an 81.2% yield.[221]

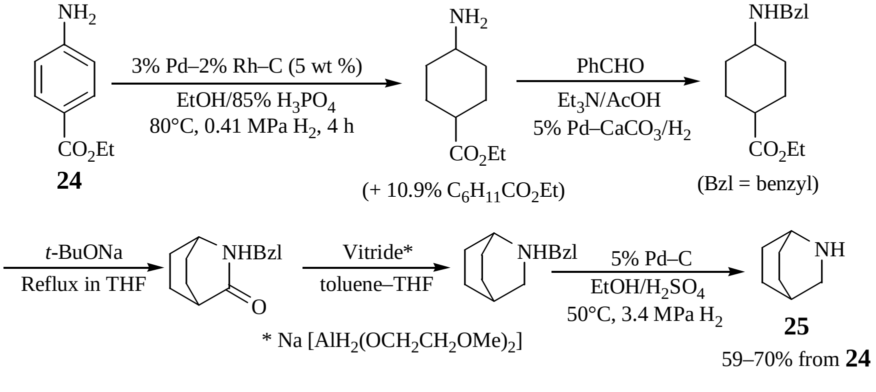
Hydrogenation of *p*-aminobenzoic acid to a mixture of *cis*- and *trans*-4-aminocyclohexanecarboxylic acid was successful with the use of a Rh–Pd–C catalyst (10% Rh–0.1% Pd) in water at room temperature and a low hydrogen pressure (eq. 11.65).[222] The *cis* isomer of the amino acid was further converted to 3-isoquinuclidone (2-azabicyclo[2.2.2]octan-3-one] (**23**) by heating in boiling Dowtherm A (258°C).



(11.65)

Scaros et al. improved this process for the synthesis of isoquinuclidine (2-azabicyclo[2.2.2]octane) (**25**) by the reaction sequence outlined in Scheme 11.13.[223] Ethyl *p*-aminobenzoate (**24**) was hydrogenated, instead of *p*-aminobenzoic acid, since the resulting amino ester cyclized at a lower temperature than did the amino acid. The use of 3% Pd–2% Rh–C was advantageous in that, at low catalyst loadings, the rate of hydrogenation was higher than with 5% Rh–C and the degree of hydrogenolysis (formation of cyclohexanecarboxylic acid) was not affected by increasing the temperature from 60 to 80°C. By the alkaline ring closure, the *trans* isomer as well as the *cis* isomer could be utilized for the synthesis of **25**.

From an industrial interest in the fibers and coatings areas, a number of studies on the hydrogenation of bis(4-aminophenyl)methane (4,4′-methylenebisbenzenamine) (**22**, eq. 11.63) have been described in the literature.[224] Compared to the hydrogenation of simple aromatic amines, the hydrogenation of **22** to bis(4-aminocyclo-

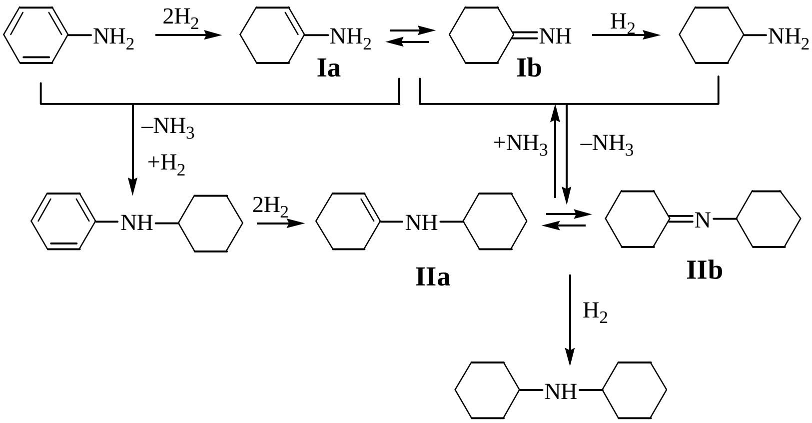


Scheme 11.13 An improved synthesis of isoquinuclidine from ethyl *p*-aminobenzoate.

hexyl)methane proceeds with much more difficulty. Barkdoll et al. found that ruthenium dioxide was very effective for this hydrogenation at 100–120°C and 13.3–20 MPa H_2 in dioxane and gave yields as high as 92% of the saturated diamine.[209] An alkali-promoted cobatic oxide, Co_3O_4–CaO–Na_2CO_3, was also effective and gave an 86% yield of the saturated diamine, but it required a much higher temperature (215°C) and a longer reaction time. The products over ruthenium dioxide at 100–120°C contained only a relatively small portion of the *trans–trans* isomer; the remainder was a mixture of *cis–cis* and *cis–trans* isomers, while the major component produced over the alkali-promoted cobalt catalyst at 215°C was the *trans–trans* isomer, with only a small quantity of the *cis–cis* isomer.[209] In one patent, transition metal sulfates, carboxylates, phosphates, or lanthanide salts are claimed to be effective as promoters for Ru–Al_2O_3-catalyzed hydrogenation of **22**, reducing the induction period and formation of high-boiling byproducts, and increasing the rate of hydrogenation.[225] Thus, with $FeSO_4 \cdot 7H_2O$ as promoter, **22** was hydrogenated over Ru–Al_2O_3 in dioxane at 125°C and 10.3 MPa H_2 to give 10.8% of *p*-(4-aminocyclohexylmethyl)aniline and 87.2% of bis(4-aminocyclohexyl)methane with only 0.1% of high boilers. Watanabe et al. hydrogenated **22** over 5% Ir-Al_2O_3 in dioxane at 120°C and 2.9–4.9 MPa H_2 to give 88% of the saturated diamine (a mixture of 25% *trans–trans*, 50% *cis–trans*, and 22% *cis–cis* isomers) and 10% of the half-hydrogenated diamine, *p*-(4-aminocyclohexylmethyl)aniline, which was further hydrogenated at 80°C to give 99% yield of the saturated diamine.[226]

Aniline has also been hydrogenated in acidic media or as its hydrochloride salt over platinum,[87,227,228] rhodium–platinum,[202] and palladium[229] catalysts. Under these conditions, the hydrogenation is usually accompanied by the formation of dicylcohexylamine, the extent of which depends on the catalyst and conditions employed. Over platinum in acetic acid, dicyclohexylamine rather than cyclohexylamine was the major product.[227,228] Ikedate et al. found that the hydrogenation of aniline in acetic acid over a 5% Pd–C at 50°C and 1 atm H_2 was accompanied by the formation of a large quantity (60% based on starting aniline) of *N*-cyclohexylaniline, which was considered to result from the addition of aniline to the enamine or imine intermediate **Ia** or **Ib** (Scheme 11.14), followed by loss of ammonia and hydrogen addition. On complete hydrogenation, dicyclohexylamine was obtained in only 30% yield (based on starting aniline). From these results, it was concluded that about 30% of cyclohexylamine in the final product had been formed through *N*-cyclohexylaniline as intermediate. This route to cyclohexylamine was confirmed by the fact that the hydrogenation of *N*-cyclohexylaniline in the presence of ammonium acetate gave dicyclohexylamine in only 45–50% yields, while in the absence of ammonium acetate *N*-cyclohexylaniline was almost quantitatively converted to dicyclohexylamine. The results were explained by the reaction pathways shown in Scheme 11.14. Ammonia may add to the enamine or imine intermediate **IIa** or **IIb**, formed from *N*-cyclohexylaniline, and the resulting adduct may be decomposed into **Ib** and cyclohexylamine. This competes with the hydrogenation of **IIb** to give dicyclohexylamine.[230]

Nishimura et al. studied the hydrogenation of isomeric anisidines over Pd–C, rhodium, and Pt–C in acetic acid at 60°C and 8.8 MPa H_2.[231] Over Pd–C, *m*-anisidine was



Scheme 11.14 Hydrogenation pathways of aniline over Pd–C in acetic acid.

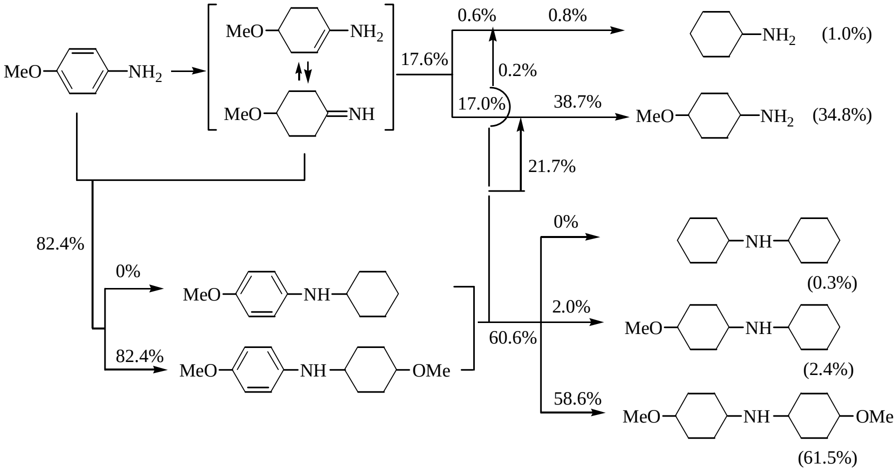
hydrogenolyzed extensively (92.5%), while the amount of hydrogenolysis was only 2.1 and 2.5% with *o*- and *p*-anisidine, respectively. Such great differences in the degree of hydrogenolysis between the isomers were not observed with rhodium and platinum catalysts (Table 11.18).

Extensive hydrogenolysis in the *meta* isomer and only slight hydrogenolysis in the *ortho* and *para* isomers over Pd–C has been explained by a very high selectivity for the formation of the enamine or imine intermediates over Pd–C, which was indicated by the formation of *N*-cyclohexylanisidine intermediates in very high selectivities (97.4% for *m*-anisidine and 82.4% for *p*-anisidine), as estimated by an extrapolation method. It is also noted that complete loss of the methoxyl group was observed in the cyclohexyl moiety of *N*-cyclohexyl-*m*-anisidine intermediate, whereas there was no such loss of methoxyl group in the corresponding intermediate from *p*-anisidine. Quite different behaviors with respect to hydrogenolysis between the *meta* and *para* isomers and the pathway to yield cyclohexylamine were also observed in the hydrogenation

TABLE 11.18 Proportion of Hydrogenolysis in the Hydrogenation of Isomeric Anisidines in Acetic Acid (%)[a,b]

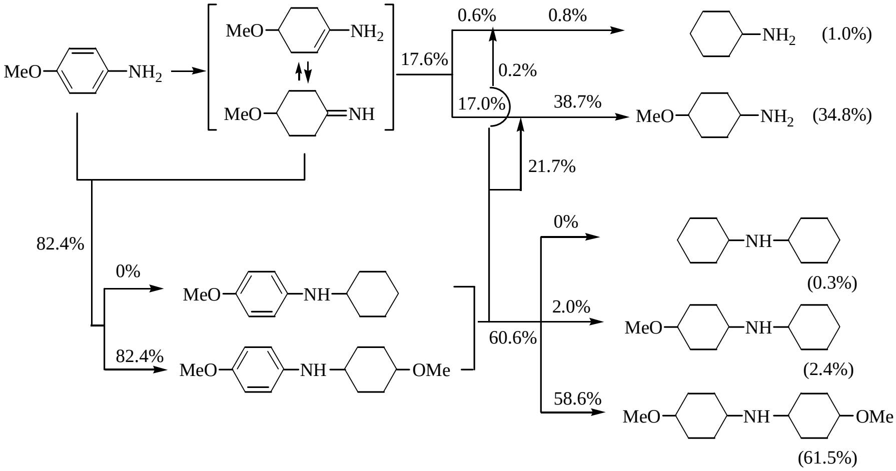
	Anisidine Hydrogenated		
Catalyst	*Ortho*	*Meta*	*Para*
Pd–C	2.1	92.5	2.6
Rh	7.7	21.5	13.9
Pt–C	—	64.5[c]	57.9[d]

[a]Data of Nishimura, S.; Takaoka, T.; Maekawa, Y. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 3648. Reprinted with permission from Chemical Society of Japan.
[b]The anisidine (0.03 mol) was hydrogenated in 15 ml acetic acid at 60°C and 8.8 ± 1.0 MPa H_2.
[c]At 60% ring hydrogenation.
[d]At 75.9% ring hydrogenation.



Scheme 11.15 Estimated hydrogenation pathways of *m*-anisidine over Pd–C in acetic acid (60°C and 8.2 MPa H_2); the figures in parentheses indicate the observed composition of the products.

of *N*-cyclohexyl-*m*-anisidine and *N*-(4-methoxycyclohexyl)-*p*-anisidine over Pd–C in the presence of an equimolar amount of ammonium acetate. On the basis of the results described above, the hydrogenation pathways of *m*- and *p*-anisidines over Pd–C in acetic acid have been estimated quantitatively as shown in Schemes 11.15 and 11.16,



Scheme 11.16 Estimated hydrogenation pathways of *p*-anisidine over Pd–C in acetic acid (60°C and 8.8 MPa H_2); the figures in parentheses indicate the observed composition of the products.

respectively. The preferential reaction of the imine intermediates with anisidines, rather than with cyclohexylamines, to yield the coupled intermediates may result from the fact that anisidines are much weaker bases (pK_a = 4.2, 5.3 for *m*- and *p*-anisidine, respectively) than cyclohexylamine (pK_a = 10.6) and therefore anisidines are much more weakly protonated in acetic acid than cyclohexylamine. Thus, in acetic acid, anisidines may react with the imines much more favorably as a nucleophile than cyclohexylamine.

Diphenylamine was hydrogenated to dicyclohexylamine as its hydrochloride salt over Adams platinum in ethanol at 30°C and 0.3 MPa H_2, while the hydrogenation of triphenylamine in the presence of hydrochloric acid gave a mixture of 50–60% of tricyclohexylamine, 8–10% of dicyclohexylamine, and cyclohexane.[228]

11.6 NAPHTHALENE AND ITS DERIVATIVES

Naphthalene is usually hydrogenated to decahydronaphthalene (decalin) via tetrahydronaphthalene (tetralin) as intermediate. Usually, the hydrogenation to tetralin proceeds more readily than the hydrogenation to decalin. This comes from the circumstances that naphthalene loses only 105 kJ (25 kcal) · mol^{-1} of the resonance energy for the hydrogenation to tetralin, while the hydrogenation of tetralin to decalin is accompanied by a loss of the resonance energy as large as 151 kJ (36 kcal) · mol^{-1}. Accordingly, naphthalene may be hydrogenated with a high selectivity to tetralin under rather mild conditions or in the presence of catalyst poisons at higher temperatures. For example, naphthalene is hydrogenated to tetralin almost quantitatively over Raney Ni at 100°C and 10–20 MPa H_2. However, further hydrogenation to decalin may begin also at 100°C; therefore, if tetralin is a desired product, the hydrogenation must be interrupted after the uptake of 2 equiv of hydrogen. On the other hand, over copper–chromium oxide, tetralin is quite stable at 200°C and is produced quantitatively in the hydrogenation of naphthalene at 200°C.[116] The results that, in the hydrogenation of naphthalene over nickel catalyst, tetralin was formed at temperatures even higher than 200°C whereas tetralin was hydrogenated to decalin at lower temperatures,[232,233] suggest that the naphthalene subjected to hydrogenation contained some catalyst poisons while the tetralin did not. Among the platinum metals, palladium catalysts are known to be highly selective for the hydrogenation of naphthalene to tetralin. In the hydrogenation of naphthalene in cyclohexane at 115–120°C and 6.9 MPa H_2 using carbon-supported palladium, platinum, rhodium, and iridium catalysts, only the hydrogenation over Pd–C stopped spontaneously at the tetralin stage.[55] According to Weitkamp, 0.6% Pd–Al_2O_3 was more selective than Pd–C in the hydrogenation of naphthalene at 100°C and an initial hydrogen pressure of 6.8 MPa, and gave the product consisting of 0.1% naphthalene, 99.7% tetralin, and 0.2% decalin.[234]

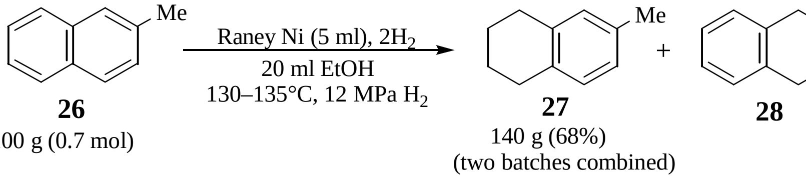
Hydrogenation of naphthalene gives a mixture of *cis*- and *trans*-decalins, the proportion of which depends largely on the nature of catalyst as well as on reaction conditions. In vapor-phase hydrogenation of naphthalene over nickel catalyst, *trans*-decalin is formed predominantly, while high-pressure hydrogenation in the liquid phase usually gives the *cis* isomer in excess. Kagehira found 10% *trans*-decalin in

the product from the hydrogenation of naphthalene over nickel catalyst at 160°C and 9.1 MPa H_2.[232] Hydrogenations over platinum catalysts always afford products rich in the *cis* isomer.[235,236]

Usually *cis*-decalin is formed more selectively from tetralin than from naphthalene. Baker and Schuetz obtained a mixture of 77% *cis*- and 23% *trans*-decalin in the hydrogenation of naphthalene over Adams platinum oxide in acetic acid–ether at 25°C and 12.8 MPa H_2, while *cis*-decalin was obtained exclusively in the hydrogenation of tetralin in acetic acid under similar conditions.[23]

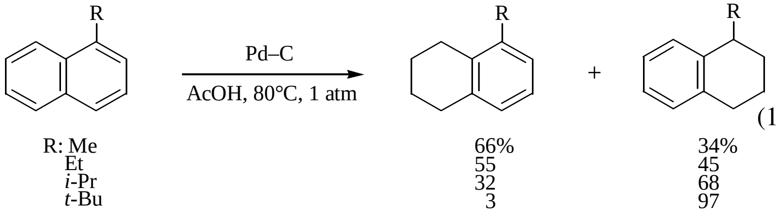
Weitkamp hydrogenated naphthalene and tetralin over supported platinum metals at 6.8 MPa H_2.[234] The selectivity of the catalysts for formation of *trans*-decalin from naphthalene decreased in the following order: Pd–C (52%) (at 100°C) > Rh–Al_2O_3 (~17.5%) (at 25°C) > Pt–Al_2O_3 (~12%) (at 200°C) > Ir–C (~8%) (at 25°C) > Ru–C (5%) (at 25°C). The selectivity for *trans*-decalin from tetralin (25°C) was in the order Pd–C (53%) > Pt–C (16%) > Rh–C (11%) > Ir–C (7.5%) > Ru–C (5.5%). Thus, Ru–C was the most selective for the formation of *cis*-decalin and Ir–C was slightly less selective than Ru–C, while definitely larger amounts of *trans*-decalin were formed over Pd–C.

Partial hydrogenation of substituted naphthalenes may lead to the formation of two different tetralins. In the hydrogenation of 2-methylnaphthalene (**26**) over Raney Ni at 130–135°C and 12 MPa H_2, the unsubstituted ring is hydrogenated more readily to give 6-methyltetralin (**27**) in excess (eq. 11.66).[237] In the hydrogenation over supported platinum group catalysts at 100°C and ~7 MPa H_2, the ratio of the tetralins **27/28** was 4.0 over 0.6% Ru–Al_2O_3, 3.7 over 0.6% Rh–Al_2O_3, 3.0 over 5% Pd–C, and 1.3 over 0.6% Pd–Al_2O_3.[234] It is of interest that 0.6% Pd–Al_2O_3, which was a highly selective catalyst for the formation of tetralin, gave the smallest ratio of **27/28**.

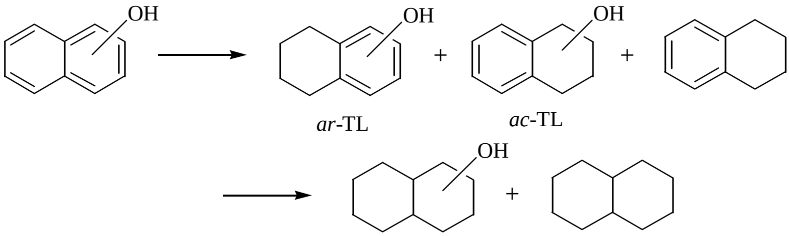


(11.66)

In the hydrogenation of 1-alkyl-substituted naphthalenes over Pd–C, the proportion of hydrogenation of the substituted ring increases with increasing bulkiness of the 1-alkyl groups, as shown in eq. 11.67.[238] The effect of the substituents is most pronounced in 1-*t*-butylnaphthalene, where the ring with *t*-butyl was hydrogenated



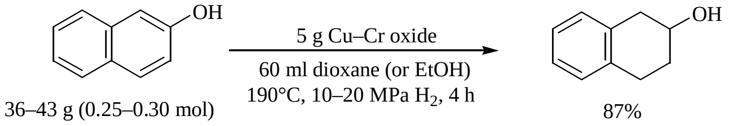
(11.67)



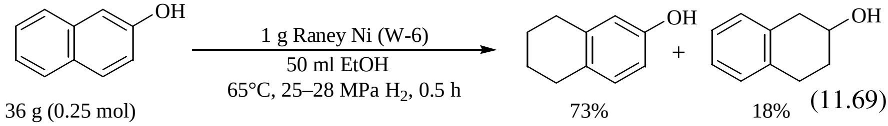
Scheme 11.17 Hydrogenation pathways of naphthols.

preferentially in 97% selectivity. The results have been explained by the release of *peri* strain in the transition state of hydrogenation, which is responsible for increasing the rate of the hydrogenation of the ring with a bulky 1-substituent.

Naphthols are hydrogenated to decahydronaphthols (decalols), usually via 5,6,7,8-tetrahydronaphthols (*ar*-tetralols or *ar*-TLs) or 1,2,3,4-tetrahydronaphthols (*ac*-tetralols or *ac*-TLs). The hydrogenation may also be accompanied by hydrogenolysis to give tetralin or decalin (Scheme 11.17). The formation of tetralin or decalin is more favored in the case of 1-naphthol than in 2-naphthol, since an intermediate *ac*-1-tetralol (*ac*-1-TL) from 1-naphthol is a benzyl-type alcohol, which is more susceptible to hydrogenolysis than *ac*-2-tetralol (*ac*-2-TL), a homobenzyl-type alcohol, from 2-naphthol. According to Musser and Adkins, copper–chromium oxide is definitely more selective than Raney Ni for the hydrogenation of the phenol ring.[116] Thus, the ratio *ar*-1-TL: *ac*-1-TL was 1:2 over copper–chromium oxide at 190°C and 10–35 MPa H_2, instead of 5:3 over Raney Ni at 155°C and 10–20 MPa H_2. In the case of 2-naphthol, the phenol ring was hydrogenated preferentially over both the catalysts, although copper–chromium oxide was more selective for the hydrogenation of the oxygenated ring. Thus, in the hydrogenation over copper–chromium oxide, *ac*-2-TL was the only product found in the reaction mixture and isolated in 87% yield (eq. 11.68).[116] In ethanol over Raney Ni, however, it is usual that the predominant product is *ar*-2-TL,[57,239,240] as in an example shown in eq. 11.69.[240]

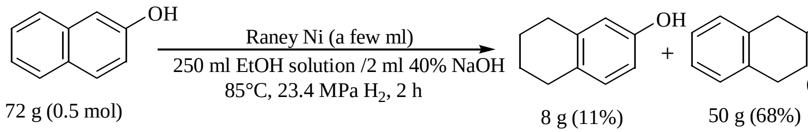


(11.68)



(11.69)

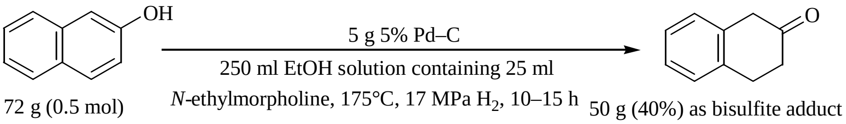
The ratio of the *ar*-2-TL/*ac*-2-TL formed, however, varies considerably with the presence or absence of alkaline substances and also with solvents. Stork showed that in the presence of small amounts of sodium hydroxide or triethylamine *ac*-2-TL was obtained in more than 60% yields in the hydrogenation over Raney Ni in ethanol (eq. 11.70), while in neutral ethanol or the ethanol acidified with addition of acetic acid *ar*-2-TL became the predominant product (57–68% yield).[239] In one patent, *ar*-2-TL was obtained in an 83.3 mol% yield by hydrogenation of 2-naphthol over Raney in EtOH–AcOH adjusted to pH 2 at 110°C and 1.96 MPa H_2.[241]



(11.70)

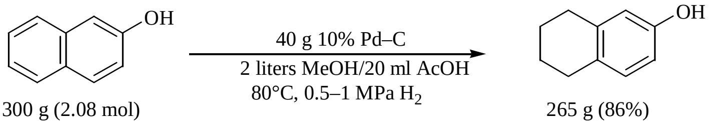
Kajitani et al. studied the effects of solvents and added amines on the selectivity for the formation of *ar*- and *ac*-2-TL in the hydrogenation of 2-naphthol over Urushibara Ni (U-Ni), Raney Ni, Urushibara Co (U-Co), and Raney Co at elevated temperatures and 4.9 MPa H_2.[242] U-Ni-B and U-Ni-A exhibited higher selectivities for the formation of *ac*-2-TL than Raney Ni, especially in alcoholic solvents. In general, the selectivity of the nickel catalysts for *ac*-2-TL increased with respect to solvents in the following order irrespective of the catalysts: *i*-PrOH < EtOH < MeOH; Et_2O < C_6H_6. The highest selectivity to *ac*-2-TL (78%) was obtained over U-Ni-B in methanol. The selectivities decreased to 53–56% in isopropyl alcohol and further to 46% in butyl ether. Over Raney Ni (well-washed W-7), the selectivity changed from 35% in methanol to 19% in isopropyl alcohol and butyl ether. The selectivities over U-Ni-A were generally between those over U-Ni-B and Raney Ni. On the other hand, the selectivity over cobalt catalysts was less extensively influenced by the solvents. The addition of amines to ethanol also affected the selectivity to a greater extent for the nickel catalysts than for the cobalt catalysts. The selectivity to *ac*-2-TL depended on the nature of added amines and increased in the order primary < secondary < tertiary amines. For example, the selectivity to *ac*-2-TL was 67% over both U-Ni-B and Raney Ni in the presence of triethylamine but decreased to 30 and 33%, respectively, in the presence of butylamine. It is noted that the addition of butylamine affected the selectivity to decrease rather than to increase or was without effect, when compared to the values without additive (62–66% with U-Ni-B and 33% with Raney Ni in ethanol).

Palladium catalysts are known to be highly selective for the formation of tetralols in the hydrogenation of naphthols because of their low activities for the hydrogenation of tetralols to decalols. As with nickel catalysts, the presence of bases promotes the hydrogenation of the phenol ring. Thus, higher than 90% selectivity to *ac*-2-TL was obtained in the hydrogenation of 2-naphthol over a 5% Pd–ZrO_2 in 3:1 ethanol–H_2O at 80°C and 4.9 MPa H_2 in the presence of a small amount of sodium hydroxide (NaOH/naphthol = 0.05 mol/mol).[243] In the presence of *N*-ethylmorpholine, 2-tetralone was obtained in 40% yield from 2-naphthol over Pd–C at 175°C and 17 MPa H_2 (eq. 11.71).[244]

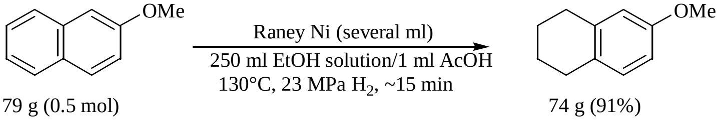


(11.71)

The presence of acetic acid increases the selectivity to *ar*-2-TL.[239] According to one patent, *ar*-2-TL was obtained in 80–86% yield and the formation of *ac*-2-TL was depressed to 0–14% in the hydrogenation over Pd–C in methanol–acetic acid (eq. 11.72).[245] A similar effect of acid was also observed in the Raney Ni catalyzed hydrogenation of 2-methoxynaphthalene where 6-methoxyteralin was obtained in 91% yield with addition of acetic acid to ethanol (eq. 11.73).[239]

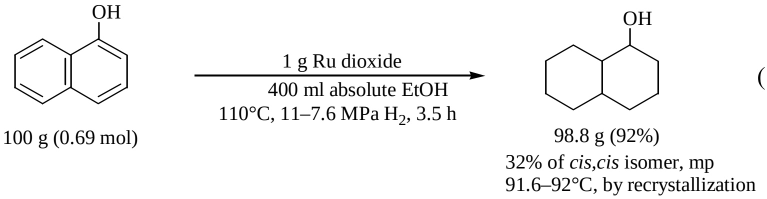


(11.72)

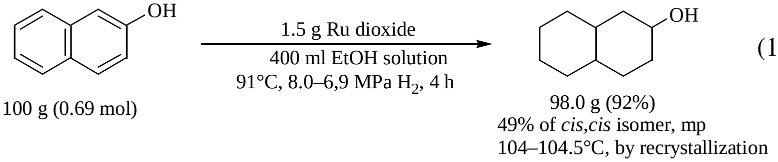


(11.73)

Hydrogenation of 1- and 2-naphthols to the corresponding decalols is labile to hydrogenolysis to give tetralin or decalins. The hydrogenations over platinum in acetic acid give a mixture of decalins and the decalols, which are rich in the *cis*,*cis* isomers.[246–248] For hydrogenation with minimum amounts of accompanying hydrogenolysis, the use of ruthenium,[249,250] rhodium,[251,252] and rhodium–platinum[166] as catalysts has proved to be effective, yielding high yields of decalols. For example, 1- and 2-naphthols were hydrogenated over ruthenium dioxide to give high yields of the corresponding decalols from which the *cis–cis* isomers were isolated in 32 and 49% yields, respectively (eqs. 11.74[249] and 11.75[250]).

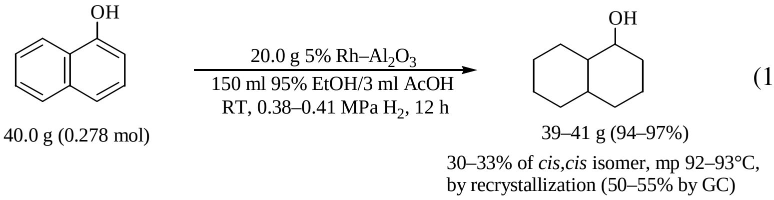


(11.74)



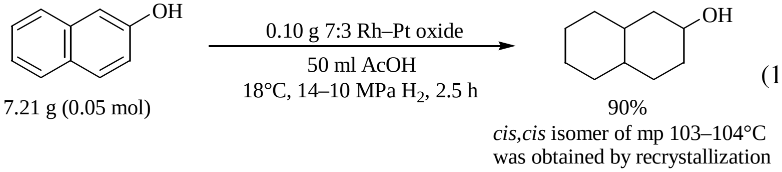
(11.75)

1-Naphthol was also hydrogenated to give high yields of 1-decalols, which were rich in the *cis,cis* isomer, over 5% Rh–Al_2O_3 in ethanol containing a small amount of acetic acid at room temperature and a low pressure of hydrogen (eq. 11.76),[251] over 5% Rh–C in ethanol at 60°C and 0.3 MPa H_2[252] or at room temperature to 46°C and 13 MPa H_2,[252] and over 7:3 rhodium–platinum oxide in acetic acid at 18°C and 13.5–11 MPa H_2.[166] Small amounts of decalins and 1-decalones were often found in the products.[251,252]



(11.76)

2-Naphthol was similarly hydrogenated to 2-decalols in 90% yield over 7:3 rhodium–platinum oxide in acetic acid (eq. 11.77).[166]



(11.77)

Nishimura et al. studied the hydrogenation of 2-naphthol (2-NL) and *ac*- and *ar*-2-tetralols (*ac*- and *ar*-2-TL) over the six platinum metals in *t*-butyl alcohol at 80°C and 4–5 MPa H_2.[91] The selectivities for *ac*- and *ar*-2-TL as well as for the products not

TABLE 11.19 Hydrogenation of 2-Naphthol over Platinum Group Metals; Selectivities for the Products[a,b]

	Selectivity for Product (mol%)[c]					
Catalyst	DN	TN	DL	2-TO	*ac*-2-TL	*ar*-2-TL
Ru	0.7	0.5	10.5	0.0	10.6	77.7
Rh	0.7	0.6	11.9	0.0	8.6	78.2
Pd–C	0.0	0.0	0.1	8.5	15.4	76.0
Os	3.1	1.1	11.0	0.0	7.2	77.6
Ir	2.0	1.3	6.0	0.0	7.2	83.5
Pt	3.8	1.4	6.0	0.0	4.9	83.9

[a] Data of Nishimura, S.; Ohbuchi, S.; Ikeno, K.; Okada, Y. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2557. Reprinted with permission from Chemical Society of Japan.

[b] 2-Naphthol (600 mg, 4.17 mmol) was hydrogenated over 4–10 mg of unsupported metal or 150 mg of 5% Pd–C in 16 ml *t*-BuOH at 80°C and 4–5 MPa H_2.

[c] DN, decalins; TN, tetralin; DL, 2-decalols; 2-TO, 2-tetralone; *ac*-2-TL, *ac*-2-tetralol; *ar*-2-TL, *ar*-2-tetralol. The selectivities for *ac*-2-TL and *ar*-2-TL were obtained by application of the equation in Scheme 11.7. The selectivities for the other products were obtained by an extrapolation method.

formed via the TLs have been determined by application of the equation in Scheme 11.7 as well as by an extrapolation method. The results thus obtained are summarized in Table 11.19.

Over all the metals, *ar*-2-TL was formed more predominantly than *ac*-2-TL, although some 9–15% of the products was formed apparently not via the TLs, except in the case of Pd–C, where the formation of the TLs was quantitative. The ratio of *ar*- to *ac*-2-TL produced (figures in parentheses) decreased in the following order with respect to catalyst metal: Pt (13.3) > Ir (9.8) > Os (9.3) > Rh (8.5) > Ru (7.0) > Pd–C (3.2). 2-Tetralone (2-TO), which was found only over Pd–C, was included in *ac*-2-TL, since 2-TO was quantitatively hydrogenated to *ac*-2-TL over Pd–C. The relative reactivities of *ac*- or *ar*-2-TL to 2-NL, *K* (*ac*-2-TL/2-NL) and *K* (*ar*-2-TL/2-NL); the rate constants for 2-NL and *ar*-2-TL in individual hydrogenations, $k_{2\text{-NL}}$ and $k_{ar\text{-2-TL}}$; the ratio of the rate constants for *ar*-2-TL and 2-NL, $k_{ar\text{-2-TL}}/k_{2\text{-NL}}$; and the ratio of the adsorption equilibrium constants for *ar*-2-TL and 2-NL, $b_{ar\text{-2-TL}}/b_{2\text{-NL}}$ are summarized in Table 11.20.

It is seen that, in general, the values of both *K*(*ac*-2-TL/2-NL) and *K* (*ar*-2-TL/2-NL) are rather small over all the metals. It is noteworthy that the values for Pd-C are extremely small, indicating a very high selectivity of Pd–C for the formation of the tetralols. The values of $k_{ar\text{-2-TL}}/k_{2\text{-NL}}$ and $b_{ar\text{-2-TL}}/b_{2\text{-NL}}$ indicate that the extremely high reactivity of Pd–C for 2-naphthol over *ar*-2-tetralol is due largely to a very small value of $k_{ar\text{-2-TL}}/k_{2\text{-NL}}$ rather than the small value of $b_{ar\text{-2-TL}}/b_{2\text{-NL}}$, which does not appear to differ much from those for the other metals. Table 11.21 compares the proportions of hydrogenolysis in the hydrogenation of 2-NL and *ac*- and *ar*-2-TLs under the same conditions.

Marked differences in the degree of hydrogenolysis can be seen between the second-row group VIII metals (Ru, Rh, Pd) and the third-row group VIII metals (Os, Ir, Pt), in particular, for 2-NL and *ar*-2-TL. It is clearly seen that the extensive hydro-

TABLE 11.20 Rate Data for Hydrogenation of 2-Naphthol and 2-Tetralols over Platinum Group Metals[a,b]

Catalyst	*K*(*ac*-2-TL/ 2-NL)	*K*(*ar*-2-TL/ 2-NL)	$10^3k_{2\text{-NL}}$ (mol · min^{-1} · g metal^{-1})	$10^3k_{ar\text{-2-TL}}$ (mol · min^{-1} · g metal^{-1})	$k_{ar\text{-2-TL}}/k_{2\text{-NL}}$	$b_{ar\text{-2-TL}}/b_{2\text{-NL}}$
Ru	0.050	0.046	19.9	6.51	0.33	0.14
Rh	0.305	0.205	22.4	20.5	0.92	0.22
Pd–C	0	0.01	9.98	0.562	0.056	0.18
Os	0.33	0.074	4.32	2.50	0.58	0.13
Ir	0.12	0.046	9.65	6.31	0.65	0.07
Pt	0.24	0.16	3.66	2.88	0.79	0.20

[a]Data of Nishimura, S.; Ohbuchi, S.; Ikeno, K.; Okada, Y. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2557. Reprinted with permission from Chemical Society of Japan.

[b]The *K* terms are the relative reactivity of *ac*- or *ar*-2-TL to 2-NL; the *k* terms are the rate constants for individual hydrogenations of 2-NL and *ar*-2-TL; *b* values represent the adsorption coefficients for 2-NL and *ar*-2-TL. 2-NL (600 mg) or 2-TL (617 mg) (4.17 mmol) was hydrogenated over 4–20 mg of unsupported metal or 150–300 mg of 5% Pd–C in 16 ml *t*-BuOH at 80°C and 4–5 MPa H_2. For the abbreviations of the compounds, see footnote *c* in Table 11.19.

TABLE 11.21 Proportions of Hydrogenolysis in the Hydrogenation of 2-Naphthol and 2-Tetralols over Platinum Group Metals[a,b]

	Proportion of Hydrogenolysis (mol%)		
Catalyst	2-Naphthol	*ac*-2-Tetralol	*ar*-2-Tetralol
Ru	2.1	0.5	0.6
Rh	2.2	1.6	1.1
Pd–C	0.2	1.6	0.2
Os	35.0	5.3	28.5
Ir	33.0	3.2	36.0
Pt	36.9	7.2	41.6

[a]Data of Nishimura, S.; Ohbuchi, S.; Ikeno, K.; Okada, Y. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2557. Reprinted with permission from Chemical Society of Japan.
[b]2-Naphthol (600 mg) or 2-tetralol (617 mg) was hydrogenated over 4–20 mg of unsupported metal or 300–400 mg of 5% Pd–C in 16 ml *t*-BuOH at 80°C and 4–5 MPa H_2.

genolysis of 2-NL over the third-row metals occurs largely via *ar*-2-TL, which is the major intermediate in the hydrogenation of 2-NL. The results on the stereochemistry of the hydrogenation of 2-NL and *ac*- and *ar*-2-TLs are summarized in Table 11.22.

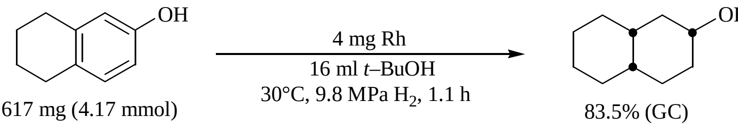
It is seen that ruthenium, osmium, and iridium are among the catalysts that give the highest selectivity for the *cis*-ring juncture products, while rhodium appears to be slightly less selective. In the hydrogenation of *ac*-2-TL, osmium and iridium show definitely higher *cis* selectivity than the other metals, in line with the results on *o*-xylene.[64] Undoubtedly, Pd–C is the catalyst that affords the largest amounts of the *trans*-ring juncture products. The selectivity for *cis,cis*-2-decalol (DL) is much higher

TABLE 11.22 The Stereochemistry of Hydrogenation of 2-Naphthol and 2-Tetralols over Platinum Group Metals[a,b]

	Products of *cis* Ring Juncture[c] (mol%)			*Cis* Isomers[d] and *cis,cis* Isomer in 2-Decalols (mol%)					
Catalyst	2-NL	*ac*-2-TL	*ar*-2-TL	2-NL		*ac*-2-TL		*ar*-2-TL	
Ru	97.5	88.0	98.9	97.7	71.0	88.0	53.0	99.0	70.6
Rh	95.1	87.1	96.1	95.5	73.1	87.2	58.6	96.2	78.6
Pd–C	65.7	51.0	68.6	65.7	52.9	51.0	28.4	68.7	58.1
Os	98.0	95.1	98.5	98.5	81.5	95.0	66.9	98.9	82.1
Ir	97.6	95.2	97.8	98.2	80.3	95.1	66.2	98.6	82.3
Pt	87.3	86.2	87.2	93.0	70.5	86.9	62.4	95.0	74.0

[a]Data of Nishimura, S.; Ohbuchi, S.; Ikeno, K.; Okada, Y. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2557. Reprinted with permission from Chemical Society of Japan.
[b]For the reaction conditions, see footnote *b* in Table 11.21. For abbreviations of the compounds, see footnote *c* in Table 11.19.
[c]The amount of *cis*-decalin and *cis,trans*- and *cis,cis*-2-decalols.
[d]*Cis,trans*- and *cis,cis*-2-decalols.

with 2-NL and *ar*-2-TL than with *ac*-2-TL, as might be expected. It is noted that the selectivity is higher over osmium and iridium than over rhodium, but the yields of the *cis,cis* isomer are much greater over rhodium (70.8 and 77.7% from 2-NL and *ar*-2-TL, respectively) than over osmium and iridium (53–59%), since extensive hydrogenolysis to decrease the yields of DLs occurs over the latter catalysts. The yield of *cis,cis*-2-DL over rhodium further increases in the hydrogenation at a lower temperature and a higher hydrogen pressure. Thus, *cis,cis*-2-DL was formed in a high yield of 83.5% in the hydrogenation of *ar*-2-TL at 30°C and 9.8 MPa H_2 (eq. 11.78).



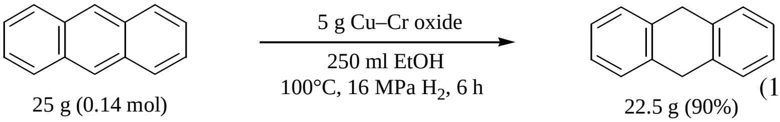
(11.78)

11.7 ANTHRACENE, PHENATHRENE, AND RELATED COMPOUNDS

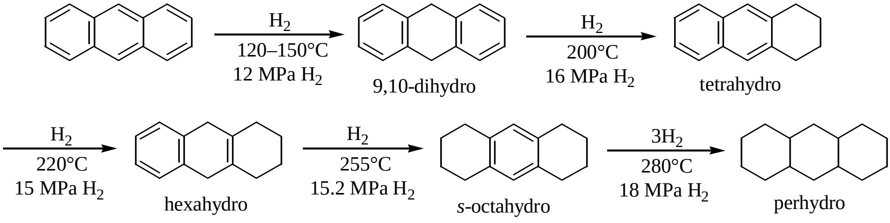
Hydrogenation of polynuclear compounds more than bicyclic may proceed via several different intermediates. Further, isomerization or disproportionation between the products may occur during the course of hydrogenation.

According to Sugino and Outi, the hydrogenation of anthracene to perhydroanthracene over reduced copper catalyst proceeds through the intermediates shown in Scheme 11.18; the formation of these compounds depends on reaction temperatures.[253]

9,10-Dihydroanthracene is obtained in high yield in the hydrogenation over copper–chromium oxide in ethanol at 100°C (eq. 11.79)[254] or in decalin at 150°C.[255] Tetrahydroanthracene is obtained in high yield in the hydrogenation over copper–chromium oxide at 240–260°C and 9.5 MPa H_2.[255]



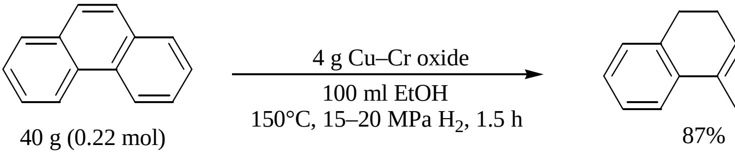
(11.79)



Scheme 11.18 Hydrogenation pathways of anthracene over reduced copper catalyst.

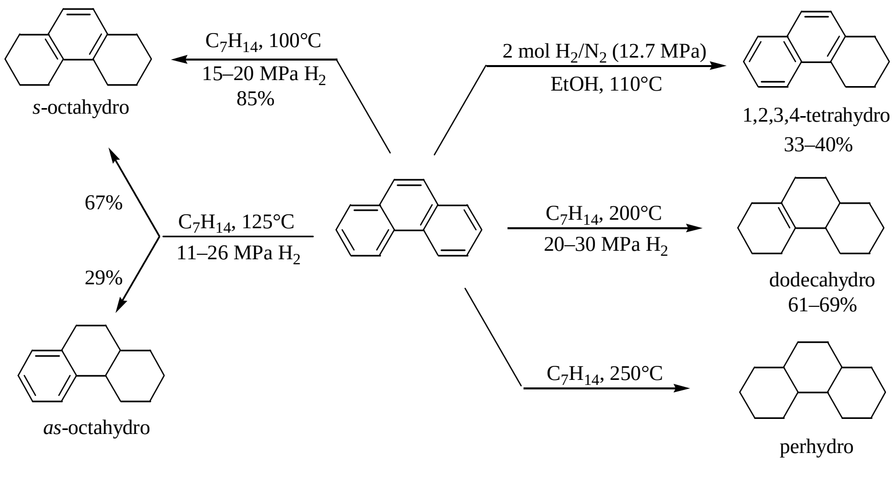
The hydrogenation of anthracene over nickel and platinum catalysts usually yields tetrahydroanthracene or further hydrogenated products in excess rather than 9,10-dihydroanthracene. Fries and Schilling concluded that the hydrogenation of anthracene over platinum oxide in acetic acid afforded 9,10-dihydroanthracene and 1,2,3,4-tetrahydroanthracene simultaneously, and the latter, the major product, was readily hydrogenated further to give *s*-octahydroanthracene.[256] The hydrogenation of anthracene to octahydroanthracenes was not difficult over nickel catalysts at elevated temperatures and pressures (e.g., at 180–220°C and 9.8 MPa H_2), but the hydrogenation to perhydroanthracene required replacement of the catalyst by a portion of fresh catalyst.[232,257]

Phenanthrene, like anthracene, is hydrogenated to the 9,10-dihydro derivative in high yield over cooper–chromium oxide. Burger and Mosettig required 220°C for this transformation,[258] but Durland and Adkins later showed that well-purified phenanthrene could be hydrogenated at 130°C and best at 150°C to give the dihydro compound in 87% yield (eq. 11.80) and at 220°C, octahydrophenanthrenes were formed as the main products.[259] At 300°C further hydrogenation to perhydrophenanthrene took place.



(11.80)

Over Raney Ni, phenanthrene may be hydrogenated to 1,2,3,4-tetrahydro-, *s*- and *as*-octahydro-, dodecahydro-, and perhydrophenanthrenes under the conditions described in Scheme 11.19.[260]

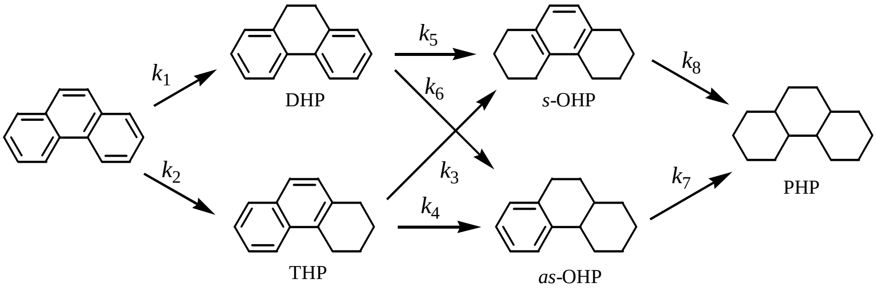


Scheme 11.19 Hydrogenation of phenanthrene to hydrophenanthrenes over Raney Ni.

Hydrogenation to 9,10-dihydrophenanthrene over Raney Ni was not as satisfactory as with copper–chromium oxide, although a 61% yield was obtained at 96°C. Hydrogenation of 9,10-dihydrophenanthrene to *s*-octahydrophenanthrene indicates that the migration of hydrogen from the 9,10-position is involved. The octahydrophenanthrenes may also undergo isomerization with the migration of hydrogen. Since the *s*-octahydro isomer is the more stable, usually this isomer tends to form in excess at high temperatures. Similar transformation of 9,10-dihydro- and 1,2,3,4-tetrahydrophenanthrenes to *s*-octahydrophenanthrene was also observed by Minabe et al. in the hydrogenation over Raney Ni in ethanol even at 50°C and 0.49 MPa H_2.[261]

Nakahara and Nishimura studied the selectivities of copper–chromium oxides, nickel, palladium, rhodium, and ruthenium catalysts in the hydrogenation of phenanthrene, 9,10-dihydrophenanthrene (DHP), and 1,2,3,4-tetrahydrophenanthrene (THP), usually in cyclohexane at 80°C (150°C for copper–chromium oxide) and an initial hydrogen pressure of 11 MPa (5 MPa for platinum metals). The hydrogenations over Os–C, Ir–C, and Pt–C were very slow and not investigated further. The varying compositions of the reaction mixture versus reaction time have been analyzed on the basis of the reaction sequences shown in Scheme 11.20 by means of a computer simulation, assuming the Langmuir–Hinshelwood mechanism.[262] The results are summarized in Table 11.23.

Over all the catalysts, hydrogenation of phenanthrene proceeded to give DHP and THP as two simultaneous products, and no other products were found at the early stages of hydrogenation. The DHP as well as THP formed were practically not hydrogenated further over copper–chromium oxide. Over the other catalysts the DHP was not totally hydrogenated until most of phenanthrene and THP had been consumed, as indicated by the very small values of the relative reactivities of DHP to THP, which were evaluated to be between 0.0 and 0.04 for the catalysts other than Pd–Al_2O_3, for which a larger value of 0.17 was obtained, although the reason for this was not clear. Copper–chromium oxides with various promoters always showed the highest selectivities for DHP (88.4–90.9%), as well documented (see eq. 11.80). The high selectivity for DHP of copper–chromium oxides was affected to only a small extent by the additives (the oxides of Ba, Ca, and Ba–Mn), as well as by the temperature (120–150°C), the hydrogen pressure (5–11 MPa), and the solvents (cyclohexane, methyl-



Scheme 11.20 The hydrogenation pathways of phenanthrene.

TABLE 11.23 Selectivity of Transition Metals in the Hydrogenation of Phenanthrene, 9,10-Dihydrophenanthrene, and 1,2,3,4-Tetrahydrophenanthrene [a,b]

	Hydrogenation of Phenanthrene		Hydrogenation of DHP		Hydrogenation of THP	
Catalyst	*S* (DHP)	*S* (THP)	S_A (*s*-OHP)	S_A (*as*-OHP)	S_B (*s*-OHP)	S_B (*as*-OHP)
Cu–Cr–Ba–Mn	90.9	9.1	—	—	—	—
P-1 Ni	81.1	18.9	28.1	71.8	88.2	11.8
Raney Ni	54.9	45.1	52.0	48.0	99.4	0.6
5% Pd–C	73.8	26.2	39.3	60.7	56.4	43.6
5% Pd–C A	52.7	47.3	41.5	58.5	78.8	21.2
5% Pd–$CaCO_3$	71.4	28.6	—	—	50.0	50.0
5% Pd–$BaSO_4$	60.0	40.0	—	—	55.6	44.4
5% Pd–Al_2O_3	66.7	33.3	—	—	75.0	25.0
5% Rh–C	30.6	69.4	15.5	84.5	82.3	17.7
5% Ru–C	42.6	57.1	—	—	89.7	10.3

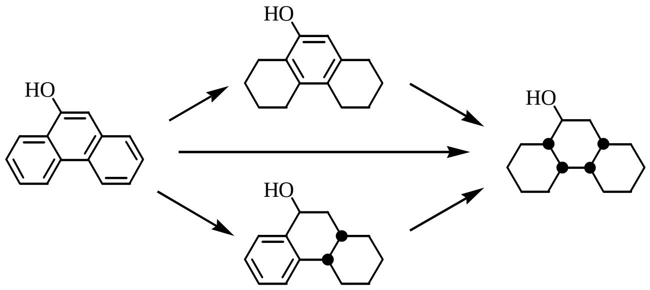
[a]Nakahara, Y.; Nishimura, S. Unpublished results; Nakahara, Y. Master's thesis, Tokyo Univ. Agric.Technol. (1993).
[b]The compound (500 mg) was hydrogenated in 18 ml cyclohexane over 200 mg of the catalyst at 80°C (150°C for Cu–Cr–Ba–Mn oxide) and the initial H_2 pressure of 11 MPa (5 MPa for the platinum group metals). The abbreviations for the compounds are: DHP, 9,10-dihydrophenanthrene; THP, 1,2,3,4-tetrahydrophenanthrene; OHP, octahydrophenanthrene. The results with THP were obtained by the analysis of the varying compositions of the products versus reaction time in the hydrogenation of phenanthrene. The *S* terms are the selectivities for the formation of the compounds shown in parentheses, given by S (DHP) = $k_1/(k_1+k_2) \times 100$; S (THP) = $k_2/(k_1+k_2) \times 100$; S_A (*s*-OHP) = $k_5/(k_5+k_6) \times 100$; S_A (*as*-OHP) = $k_6/(k_5+k_6) \times 100$; S_B (*s*-OHP) = $k_3/(k_3+k_4) \times 100$; S_B (*as*-OHP) = $k_4/(k_3+k_4) \times 100$ (see Scheme 11.20).

cyclohexane, ethanol, and *t*-butyl alcohol), although higher rates of hydrogenation were obtained at higher temperatures and hydrogen pressures and also in the hydrocarbon solvents than in alcohols. Besides copper–chromium oxides, the catalysts that showed high selectivity to DHP were P-1 Ni (77.9–81.1%) and 5% Pd–C (70.9–79.9%). The selectivity for DHP over P-2 Ni and P-1 Co was lower than over P-1 Ni, as compared in ethanol as solvent. It is noted that an acid-washed Pd–C, denoted Pd–C A, gave a much lower selectivity (52.8%) than did Pd–C, while the rate of hydrogenation of phenanthrene was nearly 6 times greater over Pd–C A than over Pd–C. It is probable that the hydrogenation over Pd–C was retarded by some basic impurities on the catalyst surface.[130] Raney Ni, Rh–C, and Ru–C were among the catalysts that gave the lowest selectivities for DHP (30.6–54.9%), and the hydrogenation to give *s*- and *as*-OHP took place over these catalysts and further to give perhydrophenanthrene (PHP) over the latter two catalysts. It is noted that the selectivity ratio for DHP and THP over Rh–C (30.6:69.4) is close to 1:2, the ratio that would result from the probability of the three benzene rings of phenanthrene in the hydrogenation. It is thus suggested that the selectivity over Rh–C is determined by a statistic factor, rather than by an energetic factor, probably due to a strong adsorption of phenanthrene to rhodium

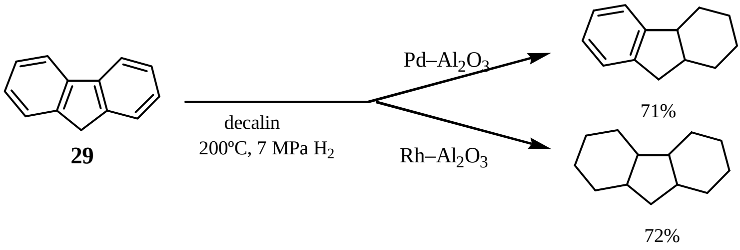
catalyst, while the selectivity over copper–chromium oxides appears to be governed chiefly by an energetic factor that may favor the formation of the product that conserves the greatest resonance energy.[263] Hydrogenations of DHP over P-1 Ni, Pd–C, and Rh–C gave *s*- and *as*-OHP as simultaneous products in which *as*-OHP was formed in excess, while over Raney Ni and Pd–C A the two OHPs were produced in comparable amounts. DHP was practically not hydrogenated over Pd–$CaCO_3$ and Pd–$BaSO_4$ at 80°C, and was extremely slow over Cu–Cr–Ba–Mn oxide even at 180°C (~1.7% conversion for 6 h). Analysis of the varying composition of product versus time in the hydrogenation of phenanthrene indicated that THP was hydrogenated to give *s*-OHP predominantly over the catalysts other than Pd–C, Pd–$CaCO_3$, and Pd–$BaSO_4$. Over the latter palladium catalysts, the two OHPs were formed almost in equal amounts. The hydrogenation of *s*-OHP was carried out with Cu–Cr–Ba–Mn oxide, P-1 Ni, Pd–C, and Rh–C. However, *s*-OHP was effectively hydrogenated only with Rh–C, over which *s*-OHP was completely converted into PHP in 6 h.

Linstead et al. obtained *cis,syn,cis*-perhydro-9-phenanthrol in the hydrogenation of 9-phenanthrol over Adams platinum oxide in acetic acid.[62] *Cis-as*-octahydro-9-phenanthrol also afforded the *cis,syn,cis* isomer preferentially. *s*-Octahydro-9-phenanthrol formed as intermediate was also considered to give the *cis,syn,cis* isomer (Scheme 11.21). The results have been explained on the basis of the following hypotheses: (1) when one or more aromatic rings are hydrogenated during a single period of adsorption, the hydrogen atoms add to one side of the molecule; and (2) the orientation of the adsorption of an aromatic molecule on the catalyst is affected by hindrance between the catalyst and the substrate.[62] Although the idea of a single period of adsorption in hypothesis 1 does not always appear to be valid, hypothesis 2, which involves the idea of catalyst hindrance, together with the idea of one sided addition of hydrogen, can explain the result that the hydrogenation of *cis-as*-octahydro-9-phenanthrol afforded the *cis,syn,cis*-perhydro derivative preferentially.

Fluorene (**29**) is converted principally into hexahydrofluorene over Pd–Al_2O_3 (71% yield) and into perhydrofluorene over Rh–Al_2O_3 (72% yield) in decalin at 200°C and 7 MPa H_2 (Scheme 11.22).[264] Pt–Al_2O_3 showed a much lower activity under the same conditions; only 2.7% of fluorene was converted, mainly to hexahydrofluorene. Treatment of fluorene with Raney Ni in refluxing toluene in the presence of triethylamine leads to exclusive formation of *cis*-hexahydrofluorene.[265]



Scheme 11.21 Stereochemistry of the hydrogenation of 9-phenanthrol and its octahydro derivatives over Adams platinum oxide in acetic acid.



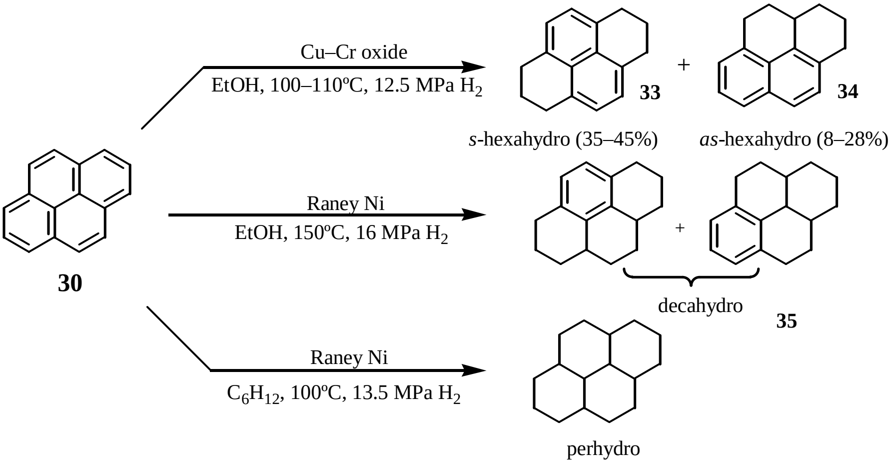
Scheme 11.22 Hydrogenation of fluorene over Pd–Al_2O_3 and Rh–Al_2O_3.

11.8 OTHER POLYNUCLEAR COMPOUNDS

Pyrene (**30**) is hydrogenated to a mixture of *s*- and *as*-hexahydroderivatives over copper–chromium oxide in ethanol at 100–110°C. Over Raney Ni, the hydrogenation in ethanol at 150°C leads to a mixture of two decahydro derivatives and the hydrogenation in cyclohexane at 100°C yields perhydropyrene (Scheme 11.23).[254]

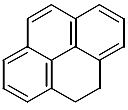
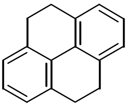
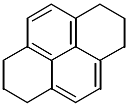
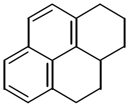
Minabe and Nakada studied the hydrogenation of pyrene over Raney Ni in ethanol at room temperature and atmospheric hydrogen pressure.[266] The selectivities to dihydro-, tetrahydro-, and hexahydropyrenes at an initial stage and after 8 h reaction are shown in Table 11.24.

It is seen that initially 4,5-dihydropyrene (**31**), 1,2,3,6,7,8-hexhydro(*s*-hexahydro)pyrene (**33**), and 1,2,3,3a,4,5-hexahydro(*as*-hexahydro)pyrene (**34**) are formed simultaneously from pyrene. The most part (78%) of initially formed **31** is hydrogenated to the tetrahydro derivative **32** rather rapidly. The hydrogenation of **32** is very slow under these conditions, and it has been shown that it is isomerized largely



Scheme 11.23 Hydrogenation of pyrene over copper–chromium oxide and Raney Ni.

TABLE 11.24 Hydrogenation of Pyrene over Raney Ni[a,b]

	Selectivity of Product (mol%)			
Reaction Time (h)	 (**31**)	 (**32**)	 (**33**)	 (**34**)
Initial stage	39	6	37	12
8	2	29	44	17

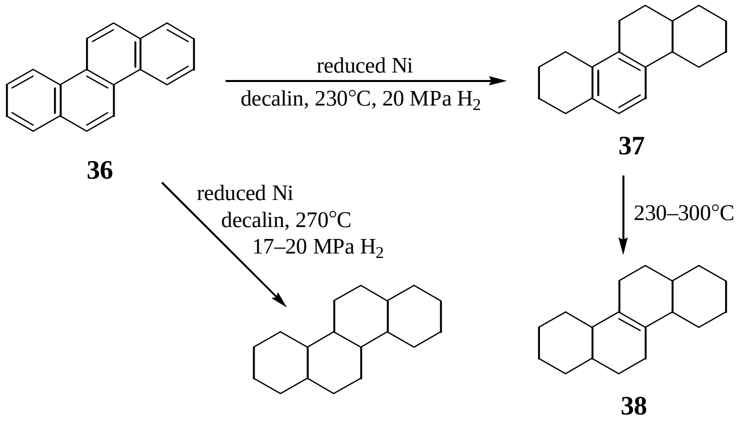
[a]Data of Minabe, M.; Nakada, K. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1962. Reprinted with permission from Chemical Society of Japan.
[b]Pyrene (202 mg, 1 mmol) was hydrogenated with Raney Ni (W-7, 0.4 g as alloy) in 40 ml ethanol at room temperature and atmospheric hydrogen pressure.

to the hexahydro derivatives **33** and **34**, although very slowly. The hydrogenation of pyrene was also studied over 10% Pd–C and platinum oxide in ethyl acetate at 50°C and 0.49 MPa H_2. The tendency in the formation of products was similar to those observed over Raney Ni, although over Pd–C the selectivity to **31** was higher (61%) than over the other catalysts, even at a 54% conversion of pyrene. Mochida et al. studied the hydrogenation of pyrene over carbon-supported palladium, platinum, rhodium, ruthenium, and rhodium–ruthenium catalysts in decalin at 150–250°C and 4.9–6.9 MPa H_2.[267] Pd–C was the most selective for the formation of dihydro- (**31**) and tetrahydropyrene (**32**), with the best yields of 48% (at 200°C and 6.9 MPa H_2 for 1 h) and 84% (at 150°C and 6.9 MPa H_2 for 16 h), respectively. For obtaining high yields of hexahydropyrenes **33** and **34**, the hydrogenation with a rapid heating to a higher reaction temperature of 300°C with use of Rh–C was favorable. Under these conditions for 2 h, **33** was produced in a yield of 52%, together with 13% of **34** and 17% of decahydropyrene **35** (see Scheme 11.23).[267]

Von Braun and Irmisch hydrogenated chrysene (**36**) over reduced nickel in decalin at 230°C and 20 MPa H_2 and obtained the dodecahydrochrysene **37**, and the hexadecahydrochrysene **38** at 230–300°C, but could not obtain the perhydro derivative.[268] Later, however, Spilker could obtain perhydrochrysene by hydrogenating a sulfur-free chrysene in decalin at 270°C and 17–20 atm H_2 (Scheme 11.24).[269]

The hydrogenation of chrysene over a 10% Pd–C catalyst at room temperature and 0.31 MPa H_2 afforded 5,6-dihydrochrysene, while over platinum oxide 1,2,3,4-tetrahydrochrysene was formed as the major product along with several minor products. 1,2,3,4,5,6-Hexahydrochrysene was obtained in 42% yield in the hydrogenation over a mixed Pd–C/platinum oxide under similar conditions (Scheme 11.25).[270]

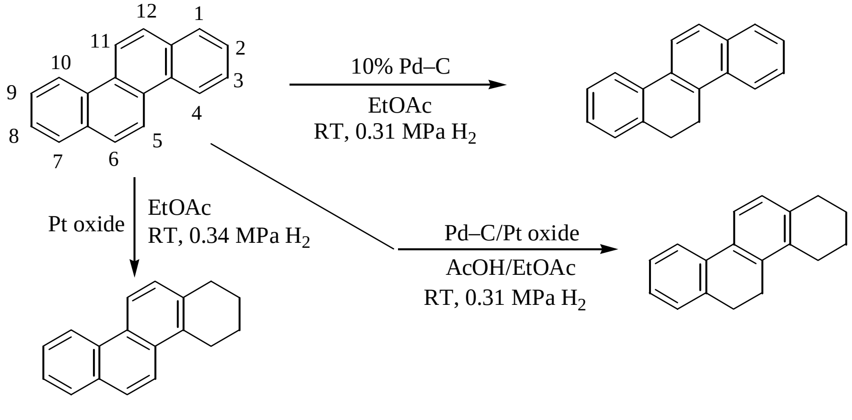
Mochida et al. studied the hydrogenation of fluoranthene (**39**) over carbon-supported platinum metal catalysts in decalin at elevated temperatures and pressures.[267] Fluoranthene was hydrogenated much more readily than pyrene, and was highly selective for the formation of tetrahydrofluoranthene **40** over all the catalysts investi-



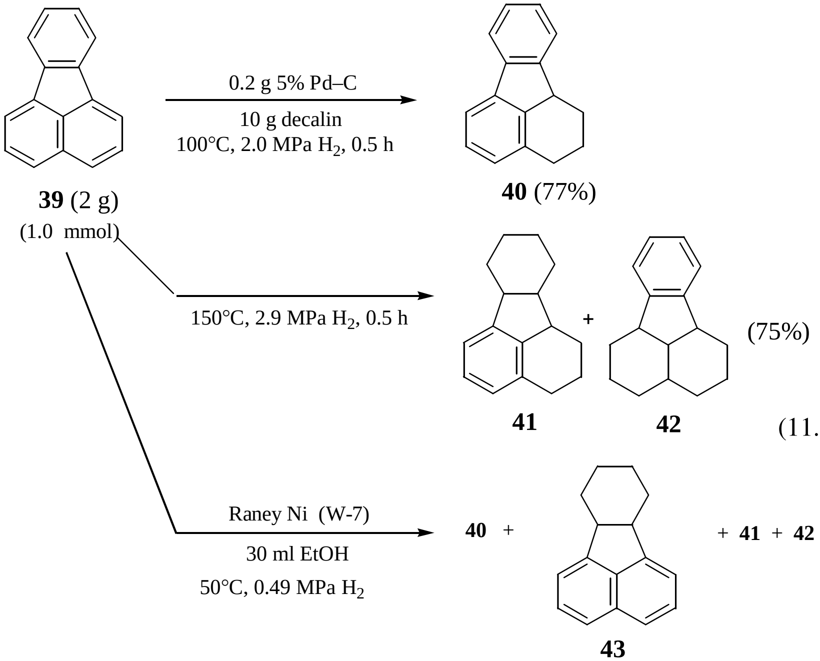
Scheme 11.24 Hydrogenation of chrysene over reduced nickel catalyst.

gated. A high yield of 77% of **40** was obtained in the hydrogenation over 5% Pd–C at 100°C and 2 MPa H_2 for 0.5 h. At 150°C and 2.9 MPa H_2, 75% of the product was decahydro derivatives **41** and **42** in 0.5 h with 100% conversion of fluoranthene (eq. 11.81). Petrov et al. studied the hydrogenation of fluoranthene and the stereochemistry of the resulting perhydro products over Pt–C.[271] All possible stereoisomers of perhydrofluoranthenes have been found to be produced. Minabe et al. hydrogenated fluoranthene over Raney Ni (W-7) at 50°C and 0.49 MPa H_2 to afford tetrahydro- (**40**), hexahydro- (**43**), and decahydrofluoranthenes (**41** and **42**).[261]

Benz[*a*]anthracene (**44**, R = H) gives the 8,9,10,11-tetrahydro derivative **45** when hydrogenated over Adams platinum in ethanol in the presence of ferrous chloride and hydrochloric acid. There was no indication that the 7,12-dihydro derivative, the alcoholysis product of the disodium compound, was an intermediate leading to **45**. The

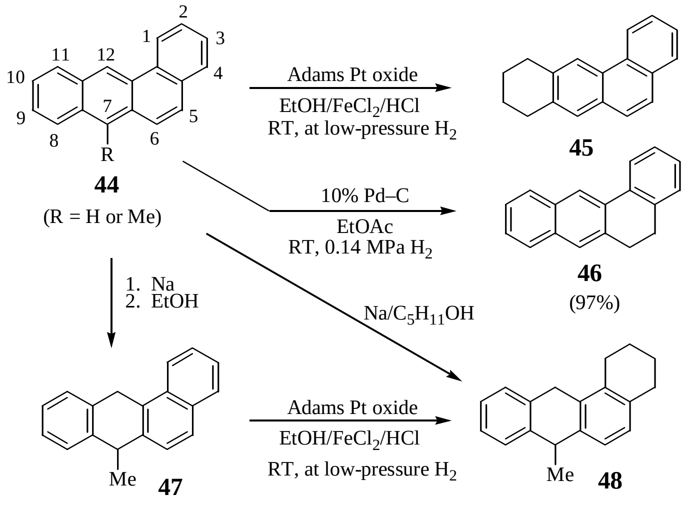


Scheme 11.25 Hydrogenation of chrysene over Pd–C, Pt oxide, and Pd–C/Pt oxide.



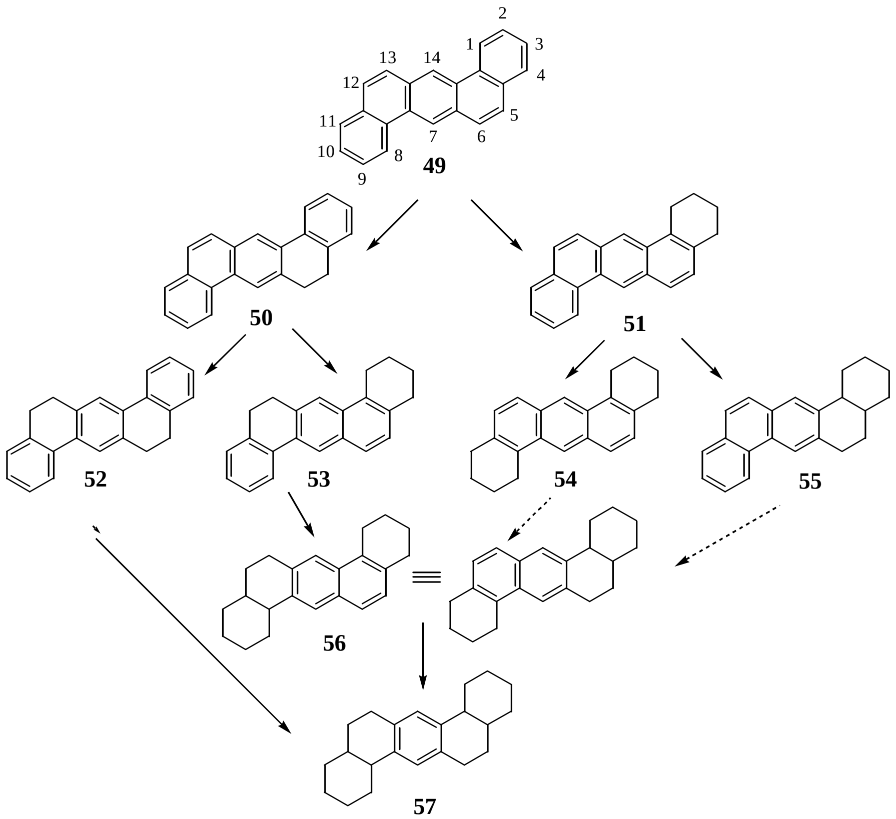
(11.81)

7,12-dihydro derivative with a methyl group in the C7 position (**47**) has been shown to give the 1,2,3,4,7,12-hexahydro derivative **48** in high yield.[272] On the other hand, the 5,6-dihydro derivative **46** is obtained in a high yield of 97% by hydrogenation with 10% Pd–C in ethyl acetate (Scheme 11.26).[273]



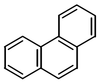
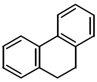
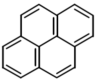
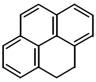
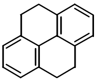
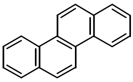
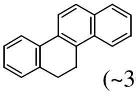
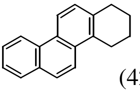
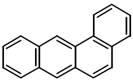
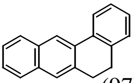
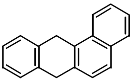
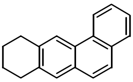
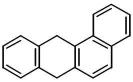
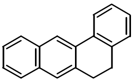
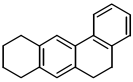
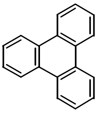
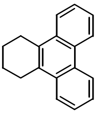
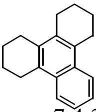
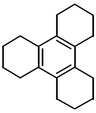
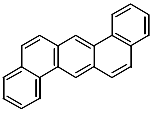
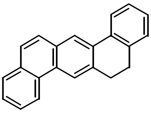
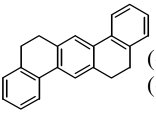
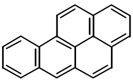
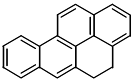
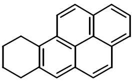
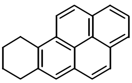
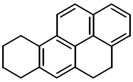
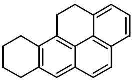
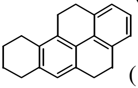
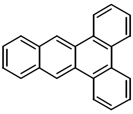
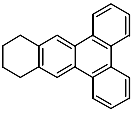
Scheme 11.26 Hydrogenation products of benz[*a*]anthracene.

Lijinsky studied the hydrogenation of dibenz[*a*,*h*]anthracene (**49**) over platinum oxide in a 1:1 mixture of 2,2,4-trimethylpentane and acetic acid at room temperature and atmospheric hydrogen pressure that proceeded as far as to give the hexadecahydro derivative **57**.[274] 5,6-Dihydro- (**50**), 1,2,3,4-tetrahydro- (**51**), 5,6,12,13-tetrahydro- (**52**), 1,2,3,4,12,13-hexahydro- (**53**), 1,2,3,4,8,9,10,11-octahydro- (**54**), 1,2,3,4,1a,4a,5,6-octahydro- (**55**), and 1,2,3,4,1a,4a,5,6,8,9,10,11-dodecahydrodibenz[*a*,*h*]anthrathene (**56**) were isolated in the yields from 3% to 25% of the reacted **49**. No product from the addition of hydrogen in the 7 and 14 positions was found in any of the hydrogenated mixtures. In the early stages of the hydrogenation (2 mol of hydrogen), a dihydo derivative, **50**, was the major product; 4–5 times as much of this compound as of the tetrahydro product **51** was present. It appeared that **51** was hydrogenated almost as readily as **49**, since **51** could not be detected after the addition of 4 mol of hydrogen. Hydrogenation of the tetrahydro derivative **52** gave the hexadecahydro derivative **57** as the sole product. The hydrogenation pathways of **49**–**57** may thus be formulated as shown in Scheme 11.27.



Scheme 11.27 Hydrogenation products of dibenz[*a*,*h*]anthracene over platinum oxide in 1:1 mixture of 2,2,4-trimethylpentane and acetic acid at room temperature and atmospheric pressure.

TABLE 11.25 Hydrogenation of Polynuclear Aromatic Hydrocarbons over Pd and Pt Catalysts[a,b]

Compound	Products (yield, %)	
	10% Pd–C	10% Pt–C or Pt oxide
	 (70)	
	 (45)  (45)	
	 (~30)	 (42)
	 (97)  (3)	 (95)  (5)
		 (85)
		   7:4:3
	  (~70)[c]:(30)[c] (~0)[d]:(~100)[d]	
	 (~100)	 (86)
	 (50)[e]  (40)[e]  (10)[e](~100)[f]	
		 (100)

[a]Data of Fu, P. P.; Lee, H. M.; Harvey, R. G. *J. Org. Chem.* **1980**, *45*, 2797. Reprinted with permission from American Chemical Society.
[b]Hydrogenations were performed in ethyl acetate at room temperature and 0.14–0.34 MPa H_2.
[c]Reaction time 5 h.
[d]Reaction time 24 h.
[e]Reaction time 18 h.
[f]Reaction time 48 h.

Fu et al. hydrogenated a number of polynuclear aromatic hydrocarbons over 10% Pd–C and platinum catalysts (10% Pt–C or platinum oxide) in ethyl acetate at room temperature and a low hydrogen pressure.[273] The results, summarized in Table 11.25, led to the conclusion that the hydrogenation of polynuclear aromatic hydrocarbons over palladium catalyst affords regiospecifically the corresponding K-region (a bond, such as the 9,10-bond of phenanthrene, excision of which leaves an intact aromatic ring system) dihydro derivatives, while over platinum catalyst the hydrogenation takes place regioselectively on terminal rings to provide the related tetrahydro derivatives.

The reactivities and selectivities of various polynuclear carbocyclic and *N*-heterocyclic aromatic compounds in the hydrogenation over transition metals have been discussed by Sakanishi et al.[264] and Minabe et al.[261]

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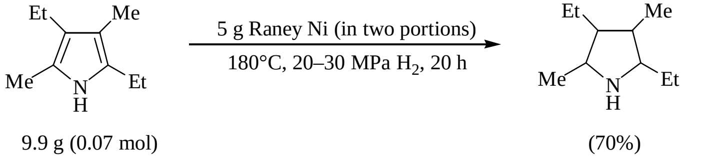
CHAPTER 12

Hydrogenation of Heterocyclic Aromatic Compounds

12.1 *N*-HETEROCYCLES

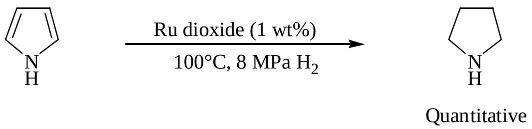
12.1.1 Pyrroles

The pyrroles are usually more resistant to hydrogenation than are the derivatives of benzene, pyridine, and furan.[1] Pyrrole itself was hydrogenated to give only about 50% yield of pyrrolidine over Ni–kieselguhr at 200°C or over Raney Ni at 180°C.[2] The reaction proceeded rapidly during the absorption of about 0.75 mol of hydrogen in one hour and then became much slower. When the reaction mixture was worked up at this stage, about half the pyrrole was recovered along with an equal amount of pyrrolidine. Further reaction led to about 50% of pyrrolidine and higher-boiling products. The hydrogenation of 2,4-diethyl-3,5-dimethylpyrrole over Raney Ni at 180°C went 80% to completion at a good rate, and a 70% yield of the corresponding pyrrolidine was obtained without the formation of high-boiling products by adding the catalyst in two portions (eq. 12.1).[2] Copper–chromium oxide requires higher temperatures of 200–250°C for hydrogenation of the pyrrole ring, and in the case of the tetraalkyl-substituted pyrrole the yield of the corresponding pyrrolidine was only 50%.



(12.1)

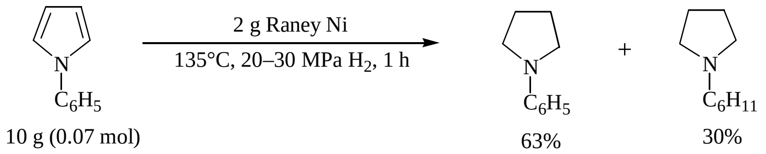
Pyrrole is hydrogenated under much milder conditions over ruthenium catalysts to give a high[3] or quantitative yield of pyrrolidine (eq. 12.2).[4]



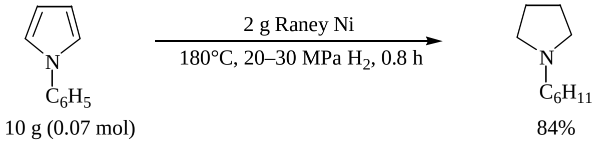
(12.2)

In contrast to the pyrroles without a substituent on the nitrogen, the *N*-substituted pyrroles are hydrogenated readily over Raney Ni at temperatures from room temperature on up to 160°C. 1-Phenylpyrrole was converted to 1-phenylpyrrolidine at 135°C and

further to 1-cyclohexylpyrrolidine at a temperature of about 180°C (eqs. 12.3 and 12.4).[2] It is noted that the *N*-substituted pyrrole ring was hydrogenated prior to the benzenoid ring.

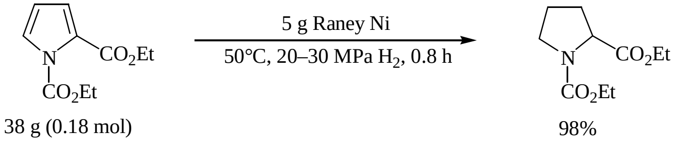


(12.3)



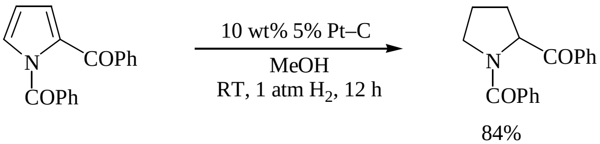
(12.4)

1-Ethoxycarbonylpyrrole was hydrogenated to the corresponding pyrrolidine in a 77% yield over Raney Ni at 160°C. The effect of the *N* substituent is particularly striking in the case of 1,2-diethoxycarbonylpyrrole, which absorbed hydrogen at room temperature and was completely converted to the corresponding pyrrolidine at 50°C (eq. 12.5).[2] In contrast, 2-ethoxycarbonylpyrrole could not be hydrogenated without affecting the ethoxycarbonyl group at any temperature.

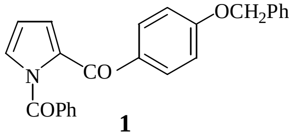


(12.5)

1,2-Dibenzoylpyrrole was hydrogenated to the corresponding pyrrolidine over either 5% Rh–C or 5% Pt–C (eq. 12.6) in methanol at room temperature and atmospheric pressure in 63 and 84% yields, respectively.[5] 1-Benzoyl-2-[4-(benzyloxy)benzoyl]pyrrole (**1**) was also hydrogenated to the corresponding pyrrolidine as the major product (66% yield) over Pt–C in methanol, whereas the hydrogenation over Rh–C in methanol–acetic acid was accompanied by the formation of the cyclohexylmethoxy compound (10%), the product hydrogenated at the benzyl group. The same hydrogenation over platinum oxide in methanol proceeded very slowly and gave the debenzylated compound as the major (62%) product.



(12.6)



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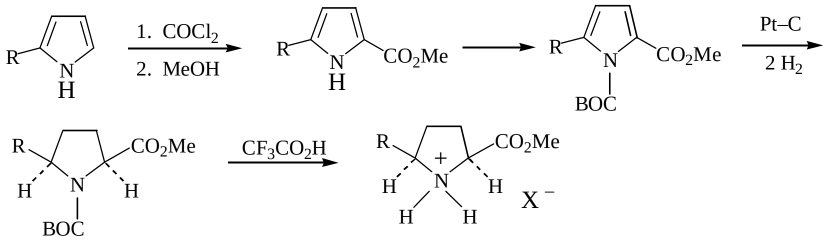
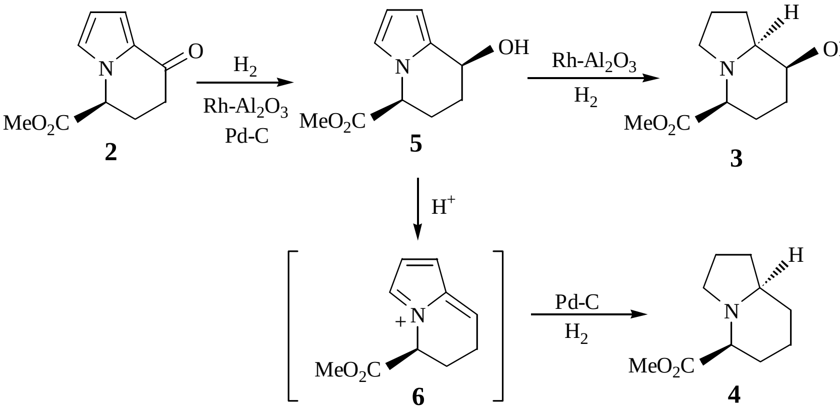


Scheme 12.1 Synthesis of 5-substituted proline derivatives from 2-substituted pyrroles (BOC = *tert*-butoxycarbonyl).

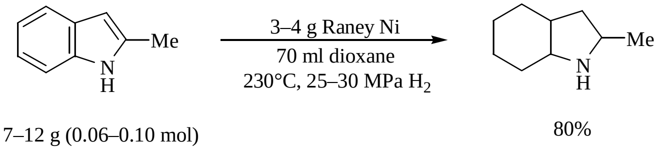
N-(*tert*-Butoxycarbonyl)pyrroles, the *N*-protecting group of which can be removed readily with trifluoroacetic acid, were hydrogenated to the corresponding pyrrolidines as the major product over 5% Pt–C. The 2,5-disubstituted pyrrolidines thus prepared were shown to be predominantly or exclusively the *cis* isomers. This catalytic hydrogenation has been applied to the synthesis of 5-substituted proline derivatives as shown in Scheme 12.1.[5] α-Ketopyrrole **2** was hydrogenated to give the corresponding indolizidine **3** diastereoselectively over Rh–Al_2O_3 in the absence of acid, while over Pd–C under acidic conditions the hydrogenolyzed indolizidine **4** was produced (Scheme 12.2).[6] From the results from hydrogenation of the possible intermediates, it has been concluded that the first step in this reduction is the hydrogenation of **2** to give the alcohol **5** with both catalysts, and an iminium ion **6** is a probable intermediate in the facile hydrogenolysis of **5** to **4**, as illustrated in Scheme 12.2.



Scheme 12.2 Hydrogenation products of α-ketopyrrole **2** over Rh–Al2O3 in the absence of acid and over Pd–C under acidic conditions.

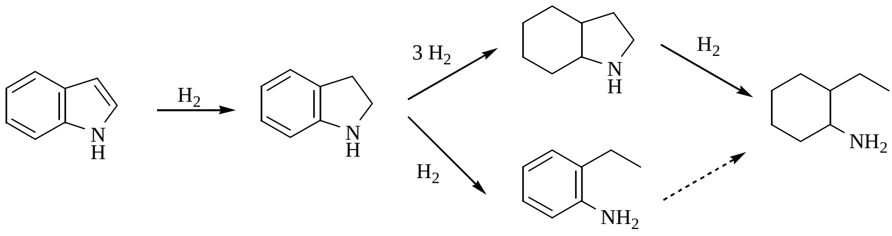
12.1.2 Indoles and Related Compounds

12.1.2.1 Hydrogenation to Perhydro Compounds. Willstätter and Jaquet hydrogenated indole to octahydroindole with a platinum black in acetic acid at room temperature.[7] Von Braun and Bayer hydrogenated indole and alkyl-substituted indoles over reduced nickel oxide in decalin at elevated temperatures and pressure.[8] Hydrogenation of indole gave 2-ethylcyclohexylamine at 200°C. 2-Methyl- and 3-methylindoles gave the corresponding octahydroindoles at 200°C and then 2-alkylcyclohexylamines at 240–250°C. Hydrogenation of 1,2-dimethylindole at 200°C gave the corresponding octahydroindole, which remained mostly unchanged at 235–240°C, with formation of only ~20% of *N*-methyl-2-propylcyclohexylamine. Thus the stability of the octahydroindoles for the ring opening appears to increase with the methyl substitution on the pyrrole ring. The formation of *o*-alkylanilines, together with the octahydroindoles and 2-alkylcyclohexylamines, indicates that hydrogenolysis of the carbon–nitrogen bond occurred at the dihydroindoles as well as at the octahydroindoles (Scheme 12.3). Adkins and Coonradt hydrogenated various indoles and dihydroindoles using Raney Ni and copper–chromium oxide as catalysts.[9] Indole, 2,3-dihydroindole, 2-methylindole (eq. 12.7), 2-methyl-2,3-dihydroindole, 3-ethylindole, and 3-ethyl-2,3-dihydroindole were all completely hydrogenated to the corresponding octahydroindoles over Raney Ni in dioxane at 220–250°C and 25–30 MPa H_2. With 2,3-dimethylindole, however, an unidentified product was obtained under these conditions.



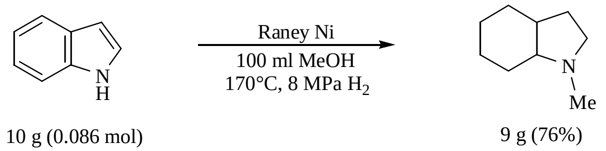
(12.7)

With Raney Ni in ethanol the hydrogenation of indole to 2,3-dihydroindole occurs quantitatively at 100–110°C and a maximum pressure of 9–10 MPa H_2, and further hydrogenation at 150–160°C gives 1-ethyloctahydroindole quantitatively. Similarly,



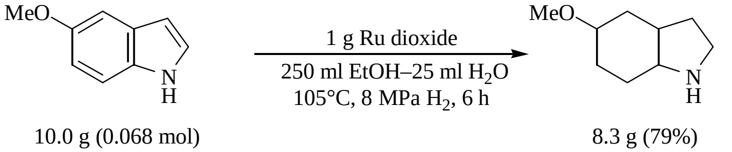
Scheme 12.3 Hydrogenation pathways of indole over nickel catalyst.

hydrogenation of indole in methanol at 170°C gave 1-methyloctahydroindole in high yield (eq. 12.8).[10]



(12.8)

Teuber and Schmitt hydrogenated 5-methoxyindole over ruthenium dioxide in 90% ethanol at elevated temperature and pressure and obtained the corresponding octahydroindole in a 79% yield (eq. 12.9).[11] The hydrogenation was difficult to complete with platinum or rhodium–platinum as catalyst in acetic acid.

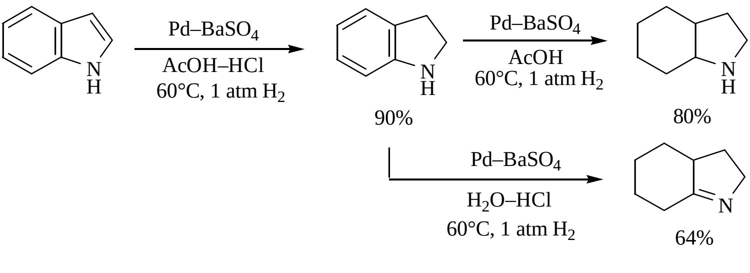


(12.9)

Over reduced $Pd(OH)_2$–$BaSO_4$, indole is hydrogenated at 60°C in AcOH–HCl to 2,3-dihydroindole, which is hydrogenated to octahydroindole in acetic acid at 60°C and to 3,3a,4,5,6,7-hexahydro-2*H*-indole in H_2O-HCl at 60°C (Scheme 12.4).[12]

Carbazole is hydrogenated to give dodecahydrocarbazole as the sole isolable product with Raney Ni in dioxane in 7 h at 230°C or in 1 h at 260°C under 25–30 MPa H_2 in 83 and 87% yields, respectively.[9] Similarly, 9-methyl- and 9-ethyldodecahydrocarbazoles were obtained in 85 and 80% yields from the corresponding carbazoles in hydrogenation at 230°C and 200°C, respectively. Carbazole was also hydrogenated to dodecahydrocarbazole in 82% yield over copper–chromium oxide in dioxane at 230°C and 25–30 MPa H_2 in 15 h.

Dressler and Baum hydrogenated carbazole with Ru–C, Rh–C, and nickel catalysts. As seen from the results shown in Table 12.1, dodecahydrocarbazole is obtained in high yields with Ru–C in decalin, with Rh–C in water (pH 5.5), and with Ni–



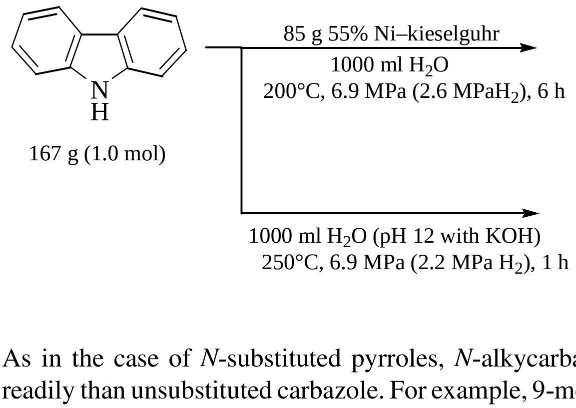
Scheme 12.4 Hydrogenation of indole and 2,3-dihydroindole over Pd–BaSO4 catalyst.

TABLE 12.1 Hydrogenation of Carbazole[a]

Catalyst	Medium	Total Pressure (MPa)	H_2 Partial Pressure (MPa)	Temperature (°C)	Main product (%)[b]
5% Ru–C[c]	Decalin	3.45	3.45	200	DHC (88)
5% Rh–C[c]	Water (pH 5.5)	6.90	2.62	200	DHC (93)
Ni–kieselguhr[d]	Water	6.90	2.62	200	DHC (88)
Sponge–Ni	Water	6.90	2.62	200	DHC (90)
Ni–kieselguhr[d]	Water (pH 12)	6.90	2.21	250	THC (87)

[a]Data of Dressler, H.; Baum, M. E. *J. Org. Chem.* **1961**, *26*, 102. Reprinted with permission from American Chemical Society.
[b]DHC: dodecahydrocarbazole; THC: 1,2,3,4-tetrahydrocarbazole.
[c]2–5 wt% of carbazole.
[d]Prereduced and stabilized nickel on kieselguhr (55% Ni).

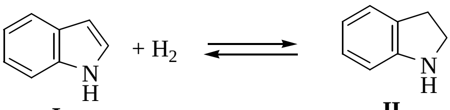
kieselguhr (eq. 12.10) or sponge nickel in water.[13] It is noted that the hydrogenation with Ni–kieselguhr in water adjusted to pH 12 with potassium hydroxide leads to the formation of 1,2,3,4-tetrahydrocarbazole (eq. 12.10), which is usually rather difficult to obtain selectively by catalytic hydrogenation.



(12.10)

As in the case of *N*-substituted pyrroles, *N*-alkycarbazoles are hydrogenated more readily than unsubstituted carbazole. For example, 9-methylcarbazole could be hydrogenated in decalin at 150–200°C and 3.45 MPa H_2 over 5% Pd–C to give an 88% yield of *N*-methyldodecahydrocarbazole, although carbazole itself was hydrogenated over the palladium catalyst in only about one fourth the rate realized with the rhodium or ruthenium catalyst under comparable conditions. Similarly, with Rh–C as catalyst, 3-amino-9-methylcarbazole was hydrogenated to the corresponding dodecahydrocarbazole in a 72% yield in water–hydrochloric acid at 50–100°C and 5.5–2.4 MPa H_2.[13]

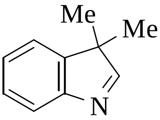
12.1.2.2 Hydrogenation to Indolines. Adkins and Coonradt observed that the hydrogenation of indole to indoline (2,3-dihydroindole) proceeded to the extent of only 70–80% over copper–chromium oxide at 170–190°C and 25 MPa H_2 and suggested that indole (**I**) and indoline (**II**) were in equilibrium under the conditions



I II

Scheme 12.5 An equilibrium between indole and 2,3-dihydroindole.

used for hydrogenation (Scheme 12.5).[9] Since the conversion of indole to octahydroindole is quite slow and essentially irreversible over copper–chromium oxide under the conditions employed (~1% conversion at 150°C and 1–2% conversion at 170°C during the establishment of equilibrium between indole and indoline), Adkins and Burks, Jr. studied the equilibria for indole, 1-methylindole, and 2,3-dimethylindole using copper–chromium oxide.[14] The extent of hydrogenation with indole was markedly affected by the pressure of hydrogen from 50% at 3.3 MPa H_2 to 91% at 35 MPa H_2 at 170°C. The values for 1-methylindole were quite similar to those for indole. However, the conversion of 2,3-dimethylindole to 2,3-dimethylindoline was much less than with indole and 1-methylindole. At an average pressure of 25 MPa H_2, the conversion to 2,3-dimethylindoline was only 35% at 170°C. In contrast, the hydrogenation of 3,3-dimethyl-3*H*-indole (**7**) (and its trimer) proceeded to completion at 3.4–4.1 MPa H_2 and the 3,3-dimethylindoline produced did not undergo dehydrogenation over copper–chromium oxide at 170°C and 3.4 MPa H_2.



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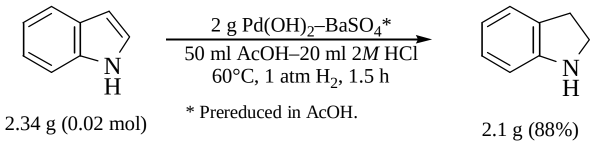
Shaw and Stapp investigated the indole–indoline equilibria using 5% Pt–Al_2O_3 as catalyst in hexadecane at 227°C and 15.2 MPa H_2.[15] The compositions of the products at equilibrium as analyzed by means of GC is shown in Table 12.2. In line with the results by Adkins and Burks, Jr., it is seen that the methyl substitution in the pyrrole ring of indole greatly affects the equilibrium concentration of indoles to increase. In particular, for 2,3-dimethylindole, the indole is more favored than the indoline at equilibrium. The existence of the indole–indoline equilibrium, as described above, necessitates the hydrogenation of indoles to be performed at temperatures as low as possible and/or in acidic medium in order to obtain the corresponding dihydroindoles in high yields. Hydrogenation at high pressures is also preferable as long as octahydroindoles are not formed.

Hydrogenation of indole with Raney Ni in ethanol at 100–110°C and 9–10 MPa H_2 has been reported to lead to the quantitative formation of indoline.[10] Hydrogenation of indole over reduced $Pd(OH)_2$-$BaSO_4$ in acetic acid–hydrochloric acid also gives indoline in high yield (eq. 12.11).[12]

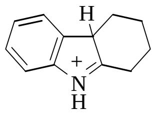
TABLE 12.2 Hydrogenation Products of Indoles over $Pt–Al_2O_3$ at 227°C and 15.2 MPa H_2[a,b]

	% Products at Equilibrium	
Indole	Indoline	Indole
Indole	82[c]	18[c]
2-Methylindole	65	35
2,3-Dimethylindole	28	72

[a]Data of Shaw, J. E.; Stapp, P. R. *J. Heterocycl. Chem.* **1987**, *24*, 1477. Reprinted with permission from the Journal of Heterocyclic Chemistry.
[b]A mixture of 0.085 mol of indole, 90 g of hexadecane, and 0.60 g of 5% $Pt–Al_2O_3$ under a hydrogen pressure of 13 MPa H_2 at room temperature was heated with rapid stirring to 227°C over 0.5 h and maintained at 227°C for 10.5 h; the final pressure at 227°C was 15.2 MPa.
[c]Indole and indoline accounted for 99% of the starting material.



(12.11)



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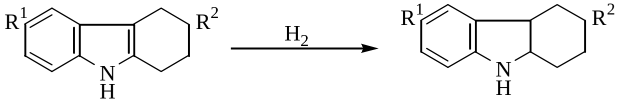
Smith and Utley hydrogenated indoles and 1,2,3,4-tetrahydrocarbazoles in about 1:1 ethanol–aqueous fluoroboric acid at room temperature and atmospheric pressure using platinum oxide as catalyst. The yields of the corresponding indolines and hexahydrocarbazoles were very high or quantitative as analyzed by GC (Table 12.3).[16] It has been suggested that the species that was subjected to hydrogenation might be the indoles protonated at the 3 position (**8**) with the C=N double bond in the indolenine system.

12.1.3 Pyridines

12.1.3.1 Pyridines. Hydrogenation of pyridines usually requires higher temperatures than those at which the benzenoid compounds are hydrogenated, although the optimal conditions may greatly depend on the nature and position of the ring substituents. Control of the temperature of hydrogenation is particularly important with pyridines because of the side reactions that may occur. According to Adkins, the side reactions are of three types: cleavage of the nitrogen–carbon linkage,

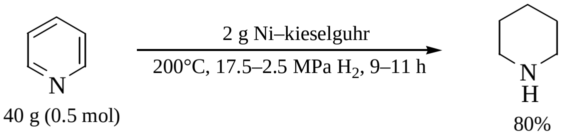
TABLE 12.3 Hydrogenation of Indoles to Indolines over Platinum Oxide in EtOH – HBF_4[a,b]



Indole					
R^1	R^2	Volume HBF_4	Volume EtOH	Reaction Time (h)[c]	Extent of Reduction (by GC) to Indoline
H	H	20	15	0.75	Quantitative
Me	H	15	10	0.70	Quantitative
H	Me	15	10	1.08	Quantitative
Me_3C	H	15	15	0.83	Quantitative
H	Me_3C	15	10	6.25	Quantitative
Indole	—	12	10	4.25	> 85%
3-Methylindole	—	15	15	5.0	> 95%

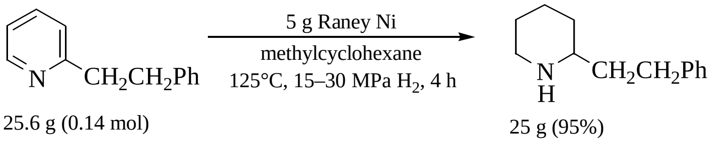
[a]Data of Smith, A.; Utley, J. H. P. *J. Chem. Soc., Chem. Commun.* **1965**, 427. Reprinted with permission from Royal Society of Chemistry.
[b]Indole (1.0g) was hydrogenated with 0.01–0.05 g of platinum oxide at room temperature and atmospheric pressure of hydrogen in ethanol and 42 w/w% aqueous fluoroboric acid.
[c]For uptake of 1 equiv of hydrogen.

alkylation at the piperidino nitrogen with use of an alcohol solvent, and condensation of various intermediate products.[17] Raney Ni is reactive at relatively low temperatures and is preferred to other nickel catalysts for the hydrogenation of pyridines. For example, 2-benzylpyridine, which required 160°C with Ni–kieselguhr, was hydrogenated over Raney Ni completely at 100°C in less than one-half the time required with the supported catalyst at 160°C.[18] Pyridine itself was hydrogenated at 200°C and 17.5–2.5 MPa H_2 over Ni–kieselguhr (eq. 12.12)[1] or at 200°C and 15–30 MPa H_2 over Raney Ni[18] without solvent. Matsumoto et al. obtained some 5–10% of high-boiling products in the hydrogenation of pyridine over Raney Ni at 190–200°C and 6 MPa H_2; the main component of these products was 1,5-dipiperidinopentane.[19] With reduced copper catalyst pyridine was hydrogenated to give only 48% yield of piperidine at 130°C and 16 MPa H_2 because of the formation of high boiling products in as high an amount as 44%.[20]



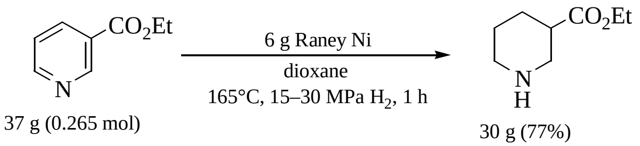
(12.12)

The substituents at the 2 and 6 positions in pyridine may facilitate hydrogenation. Thus, the pyridines with benzyl, 2-phenylethyl (eq. 12.13), or ethoxycarbonyl groups in the 2 or 2,6 positions are hydrogenated rapidly at lower temperatures than is pyridine itself.[18]



(12.13)

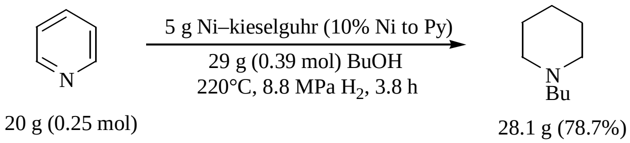
When ethyl nicotinate (3-ethoxycarbonylpyridine) was hydrogenated over Raney Ni in ethanol at 165°C, the product contained 20% of ethyl *N*-ethylnipecotate (1-ethyl-3-ethoxycarbonylpiperidine). The *N*-ethylation could be avoided when ether, methylcyclohexane, or dioxane was used as the solvent (eq. 12.14).[18] The formation of 3-methyl-2-piperidone, which amounted to a considerable amount with Ni–kieselguhr in ethanol,[21] was also never higher than 5% under these conditions. The yields of other high-boiling materials, which amounted to 15–20% in ethanol, were about 5% in methylcyclohexane or ether.



(12.14)

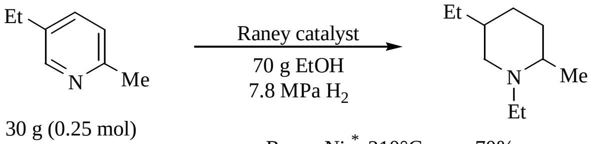
Hydrogenation of 2,3-diethoxycarbonylpyridine may be accompanied by the formation of high-molecular-weight compounds that poison nickel catalyst quite effectively. However, the diester was hydrogenated over Raney Ni in dioxane at 125°C to give a 77% of the corresponding piperidine derivative.[18]

The *N*-alkylation which accompanies the hydrogenation of pyridines in alcohols can be utilized for the preparation of *N*-alkylpiperidines.[22,23] Sawa et al. studied the *N*-alkylation of pyridine with C_1–C_{16} alcohols in the presence of Ni–kieselguhr. *N*-Butylpiperidine was obtained in a 78.7% yield when pyridine was hydrogenated in butyl alcohol at 220°C and 8.8 MPa of initial hydrogen pressure (eq. 12.15).[22] The reaction was also studied using Raney Ni and copper–chromium oxide as catalysts, resulting in somewhat lower yields of *N*-butylpiperidine.[24]



(12.15)

The *N*-alkylation was considered to occur by the reaction of the carbonyl compounds, formed by the dehydrogenation of alcohols over the catalyst, with the hydrogenation products of pyridine,[25] as suggested by Schwoegler and Adkins, who obtained good yields of *N*-alkylpiperidines by the reaction of piperidine with alcohols.[26] Maruoka et al. obtained a higher maximal yield of the *N*-ethylated product in ethanol over Raney Co than over Raney Ni in the hydrogenation of 5-ethyl-2-methylpyridine (eq. 12.16),[23] an alkylated pyridine prepared industrially by the reaction of acetaldehyde with ammonia.



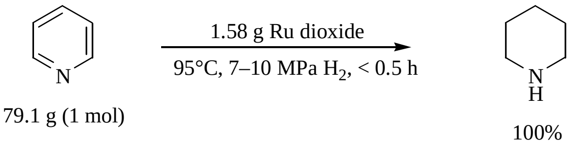
(12.16)

Raney Ni,* 210°C 70%
Raney Co,† 235°C 76%

* From 5 g of 44% Ni–Al alloy

† From 5 g of 48% Co–Al alloy.

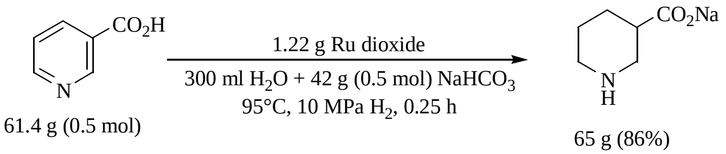
Freifelder and Stone have shown that over ruthenium dioxide, pyridine and its derivatives are readily converted to piperidines under much milder conditions (90–100°C and 7–10 MPa H_2) than required for Raney Ni catalyzed hydrogenations.[27] Thus, pyridine was hydrogenated to piperidine quantitatively at 95°C and 7–10 MPa H_2 in less than 0.5 h over 2 wt% of the ruthenium catalyst (eq. 12.17). At 200°C as little as 0.1% of the catalyst was sufficient to carry the hydrogenation to completion in little more than 1 hr.



(12.17)

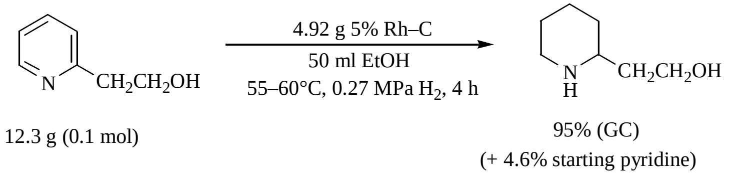
Monosubstituted pyridines were also hydrogenated rapidly under similar conditions, particularly when the substituents were nonbasic ones. With 2,4,6-trimethylpyridine, however, uptake of hydrogen was slow and it was necessary to raise the temperature to 150°C and increase the pressure to 17 MPa H_2, although the speed of hydrogen uptake was somewhat improved in methanol. In the hydrogenation of 2- and 4-benzylpyridines a strong tendency toward the formation of 2- and 4-cyclohexylmethylpiperidines was observed. Selectivity to the corresponding benzylpiperidines was difficult to control even with use of half the amount of catalyst. When an alcohol was used as solvent, there was no evidence of the *N*-alkylation, which was difficult to depress in the hydrogenations with Raney Ni owing to the use of higher temperatures. The advantage of the use of alcohols was shown in the hydrogenation of 2-(2-hydroxyethyl)pyridine where the reaction was completed when the temperature reached 90–100°C in methanol, compared to 3–4 h required without a solvent. Extensive decarboxylation, which occurred in the hydrogenation of nicotinic

acid (pyridine-3-carboxylic acid) in water, could be prevented in the presence of an equivalent of sodium hydrogen carbonate (eq. 12.18). Such decarboxylation was not observed with the other isomers. The hydrogenation of pyridines with basic side chains was retarded pronouncedly only when the amino group in the side chain was primary such as 3-aminomethyl, 2-(2-aminoethyl), and 4-(2-aminoethyl). The slow uptake of hydrogen in these compounds was considered to be due to the combined poisoning effects of the primary amino group and the piperidine nitrogen.[27]



(12.18)

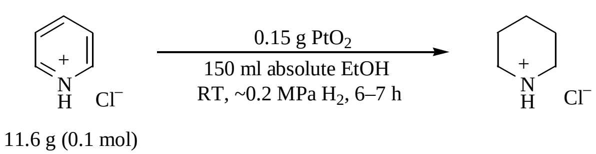
Rhodium catalysts may be applicable to the hydrogenation of pyridines at low temperature and pressure in the absence of acid.[28,29] A comparison of 5% Rh–C with 5% Rh–Al_2O_3 showed the former catalyst to be better suited for the hydrogenation of pyridines.[29] A typical example of the hydrogenation over 5% Rh–C is given in eq. 12.19 for 2-(2-hydroxyethyl)pyridine.



(12.19)

Pyridines with a substituent in the 2 position are hydrogenated faster than the corresponding 4-substituted pyridines. When 4-benzylpyridine was hydrogenated, 4-benzylpiperidine containing only a 1.25% of starting pyridine was obtained, while the hydrogenation of 2-benzylpyridine led to a mixture of 87% of 2-benzylpiperidine, 8% of 2-(cyclohexylmethyl)piperidine, and 4% of starting pyridine (GC analysis), probably because of the effect of the pyridine or piperidine nitrogen as a catalyst poison being blocked with the 2-substituent.

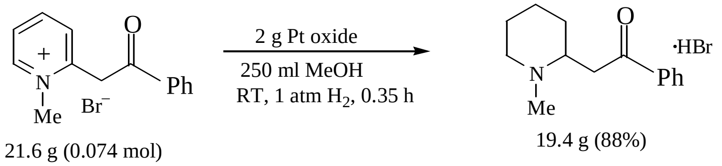
Over platinum oxide the hydrogenation of pyridine did not take place in most solvents. However, pyridine hydrochloride could be readily reduced best in absolute ethanol and second in acetic acid.[30] No satisfactory results were obtained using 95% ethanol or commercial methyl alcohol as a solvent. A typical run is given in eq. 12.20. If the temperature was raised to 50°C, the time for hydrogenation was cut to less than 2 h, compared to 6–7 h at room temperature.



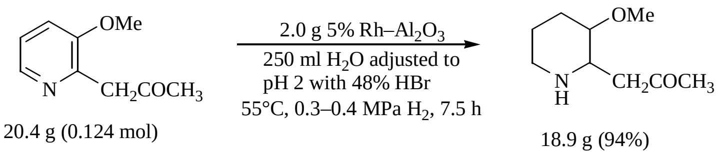
(12.20)

The quaternary pyridinium chlorides are more easily hydrogenated than pyridine hydrochloride. Thus, *N*-phenyl- and *N*-butylpyridinium chlorides were completely hy-

drogenated in 2.25–2.5 h and in 1.5–2 h, respectively, under the same conditions as in eq. 12.20.[30] Good examples of the ease of ring hydrogenation when the ring nitrogen is quaternized are seen in the selective hydrogenation of the quaternary pyridinium salts with an oxo or a cyano group in the side chain.[31–33] 1-Methyl-2-phenacylpyridinium bromide was selectively hydrogenated to 1-methyl-2-phenacylpiperidinium hydrobromide in high yield over platinum oxide in methanol without affecting the oxo group (eq. 12.21).[32] With Rh–Al_2O_3 as catalyst, however, (3-alkoxy- or 3-methyl-2-pyridyl)-2-propanones were successfully hydrogenated to the corresponding piperidylpropanones (predominating the *cis* isomers) in high yields in water in the presence of 1 equiv of hydrobromic acid.[34] A high degree of selectivity is achieved only when the substrates are carefully purified by distillation. An example is shown in eq. 12.22 for the 3-methoxy compound.

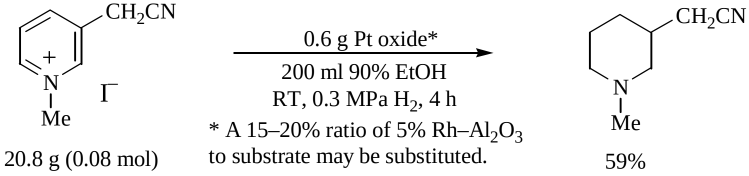


(12.21)



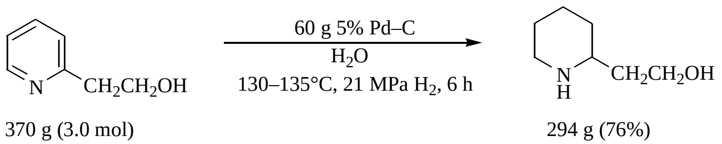
(12.22)

1-Alkyl-3-cyanomethyl- (eq. 12.23) and 1-methyl-2-(2-cyanoethyl)pyridinium iodides were also selectively hydrogenated to the corresponding cyanopiperidines in the presence of platinum oxide or Rh–C.[33] When 3-cyanomethylpyridine was hydrogenated in aqueous alcoholic hydrochloric acid or in acetic acid, the cyano group was preferentially attacked.

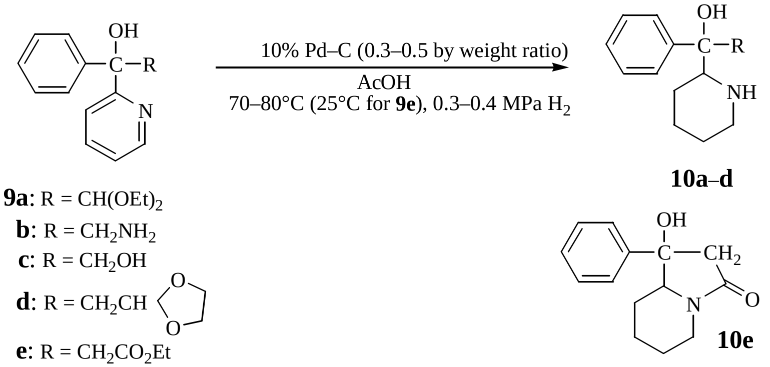


(12.23)

Some substituted pyridines are successfully hydrogenated over supported palladium catalysts. For example, 2-(2-hydroxyethyl)pyridine (eq. 12.24) and its 5-ethyl, 6-methyl, and 4,6-dimethyl derivatives were hydrogenated to the corresponding piperidines in high yields using Pd–C in aqueous solution at 130–150°C and 21 MPa H_2.[35] Walker hydrogenated various 2-substituted pyridines (**9a–9d**) to the corresponding piperidines (**10a–10d**) over 0.3–0.5 by weight ratio of 10% Pd–C in acetic acid as solvent usually at 70–80°C and 0.3–0.4 MPa H_2 (eq. 12.25).[36] The hydrogenation of **9e** led to the formation of the lactam **10e** even at 25°C.



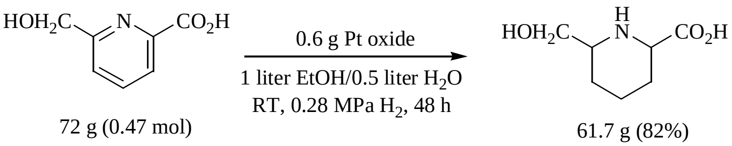
(12.24)



(12.25)

Hydrogenation of 2- and 4-phenyl- or -benzylpyridines usually occurs preferentially in the pyridine ring.[18,27,29] In trifluoroacetic acid over platinum oxide, however, 4-phenyl- and 4-(3-phenylpropyl)pyridines gave the products hydrogenated in the benzene ring in 87 and 96% yields, respectively. The hydrogenation of 2-phenylpyridine was less selective; the yield of 2-cyclohexylpyridine was 49.8%, as it was accompanied by the formation of 14.7% of 2-cyclohexyl-3,4,5,6-tetrahydropyridine, 11.2% of 2-cyclohexylpiperidine, and 10.8% of 2-phenylpiperidine, together with 13.5% of starting material.[37]

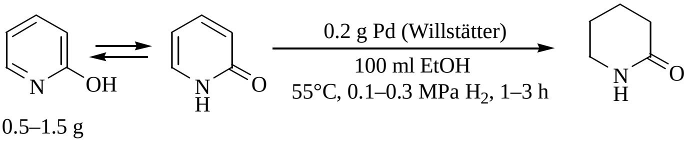
2-Hydroxymethylpyridine and substituted 2-hydroxymethylpyridines are usually hydrogenated to the corresponding piperidines without hydrogenolysis of the hydroxyl group.[38] However, Bolós et al. encountered an extensive hydrogenolysis in the hydrogenation of ethyl 6-(hydroxymethyl)-2-carboxylate and its acetate.[38] The hydrogenation with minimum hydrogenolysis with 6-hydroxymethylpyridine-2-carboxylic acid was effected with the use of platinum oxide under neutral conditions (eq. 12.26).[38]



(12.26)

12.1.3.2 Hydroxypyridines. Of the three hydroxypyridine isomers, 3-hydroxypyridine may behave as a phenolic compound, while in 2- and 4-hydroxypyridines the contribution of the corresponding tautomeric pyridones becomes important, as indicated by a great difference in their acidity between the 3-isomer (pK_a = 8.7) and the 2- and 4-isomers (pK_a = 11.6 and 11.1, respectively). Thus, the hydrogenation of 2-hydroxypyridine usually stops at 2-piperidone, a

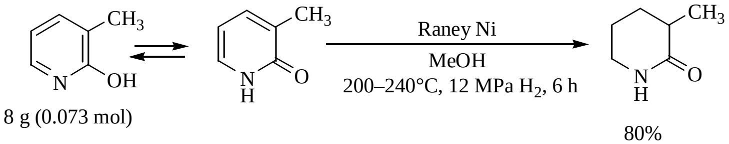
δ-lactam, which is resistant to further hydrogenation unless the conditions are too vigorous. Cavallito and Haskell were able to hydrogenate 2-hydroxypyridine to 2-piperidone with palladium black (Willstätter) in ethanol under mild conditions (eq. 12.27).[39] However, 3- and 4-hydroxypyridines were not hydrogenated under the same conditions. Adams platinum oxide or Raney Ni was ineffective in catalyzing these reactions under the conditions employed.



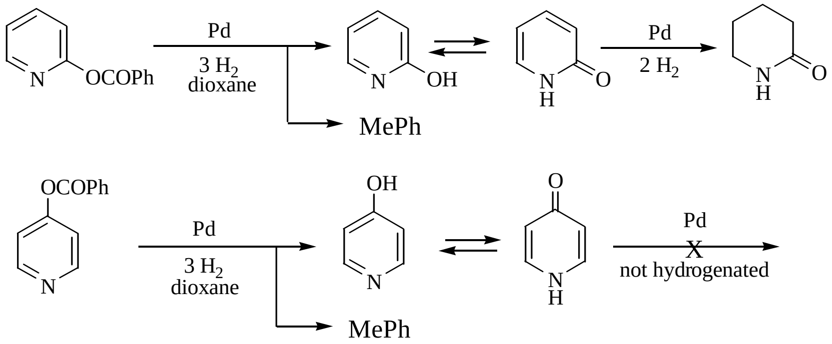
(12.27)

With the palladium black in dioxane, 2-benzoyloxy- and 2-(2-naphthoyloxy)pyridines underwent rapid hydrogenolysis to form toluene and 2-methylnaphthalene, respectively, with liberation of 2-hydroxypyridine, which was further hydrogenated to 2-piperidone. Similarly, 4-benzoyloxypyridine was readily hydrogenolyzed to give toluene and 4-hydroxypyridine, which was not hydrogenated further (Scheme 12.6). Cavallito and Haskell suggested that the unusual ease of hydrogenolysis was associated with the weakness of the aromatic ester bond.[39]

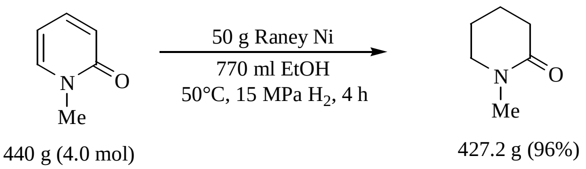
2-Hydroxy-3-methylpyridine was hydrogenated to 3-methyl-2-piperidone in an 80% yield over Raney Ni in methanol at 200–240°C and 12 MPa H_2 (eq. 12.28).[40] At 280°C, hydrogenolysis to give 3-methylpiperidine and *N*-alkylation to give 1,3-dimethylpiperidine took place. In contrast, 1-methyl-2-pyridone is hydrogenated under much milder conditions to the corresponding 2-piperidone over Raney Ni in ethanol (eq. 12.29).[41]



(12.28)

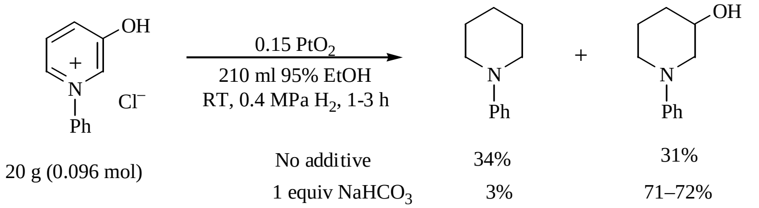


Scheme 12.6 Scheme showing the ease of hydrogenolysis in 2- and 4-benzoyloxypyridines over palladium catalyst.



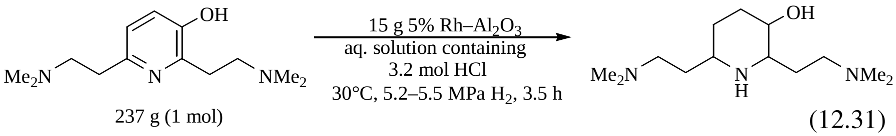
(12.29)

3- And 4-hydroxypyridines were hydrogenated to 3- and 4-hydroxypiperidines in 82 and 70.5% yields, respectively, over ruthenium dioxide in water.[42] On the other hand, hydrogenation of 3-hydroxypyridine hydrochloride[43] or 3-hydroxy-1-phenylpyridinium chloride[44] with platinum oxide in ethanol is accompanied by extensive hydrogenolysis of the hydroxyl group. Hydrogenolysis with the latter compound was largely depressed by hydrogenating in the presence of 1 equiv of sodium hydrogen carbonate (eq. 12.31).[44]



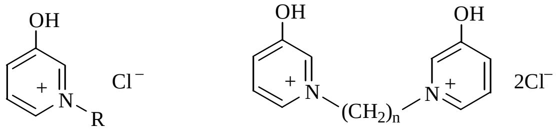
(12.30)

2-Dimethylaminomethyl-[45] and 2,6-bis(dimethylaminoethyl)-3-hydroxypyridines (eq. 12.31)[46] were hydrogenated in high yields to the corresponding 3-piperidinols over 5% Rh–Al_2O_3 in water in the presence of excess amounts of hydrochloric acid under mild conditions.

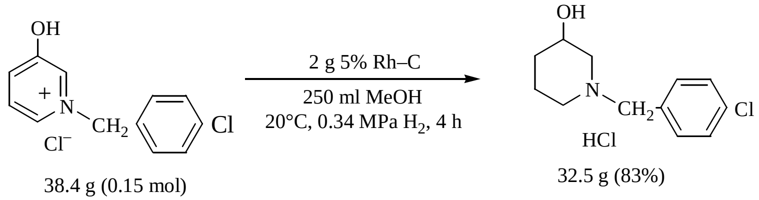


(12.31)

A number of quaternary 3-hydroxypyridinium chlorides (**11**) and α,ω-bis(3-hydroxypyridiniumo)alkane dichlorides (**12**) (as their betaines) have been hydrogenated to the corresponding piperidine derivatives over Rh–C as the catalyst.[47] A typical run with the compound **11**, R = *p*-chlorobenzyl, is shown in eq. 12.32. When platinum oxide was employed as the catalyst with the compound **12**, n = 4, hydrogenolysis to yield 1,4-bis(1-piperidino)butane took place. 3-Hydroxy-6-propylpyridine, however, was hydrogenated to 3-hydroxy-6-propylpiperidine in a 96% yield over platinum oxide in acetic acid at 20°C and 0.3 MPa H_2.[48]

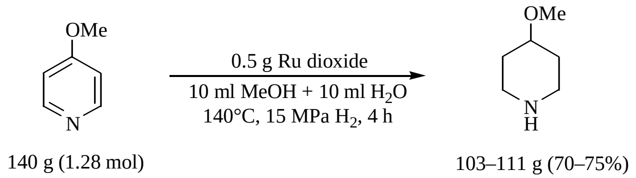


11 **12**



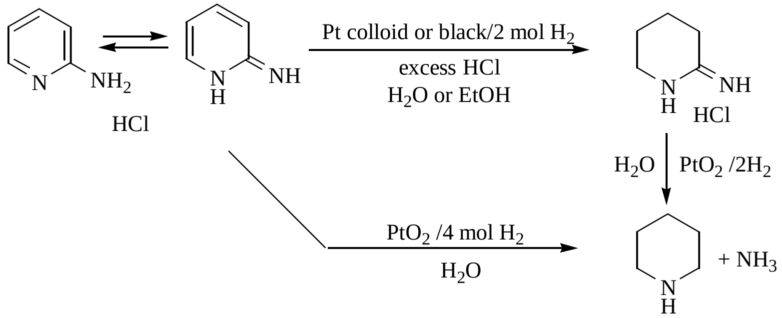
(12.32)

12.1.3.3 Alkoxypyridines. Alkoxypyridines may also be susceptible to hydrogenolysis. 2-Methoxypyridine was hydrogenated to give only piperidine in the hydrogenation over colloidal platinum in 40% acetic acid and over platinum black in aqueous or in absolute methyl alcoholic hydrogen chloride.[49] The ease of hydrogenolysis in 2-methoxypyridine probably results from the unstable carbon–oxygen bond in the >N–C–OMe moiety of the 2-methoxypiperidine formed. 3-Alkoxypyridines appear to be less labile to hydrogenolysis than do 2-alkoxypyridines.[50,51] 3-Methoxypyridine was hydrogenated to 3-methoxypiperidine in good yield over Raney Ni at 150°C and 15 MPa H_2.[50] The hydrogenation of 4-alkoxypyridines over platinum or Raney Ni was unsuccessful, and in this hydrogenation high temperatures should be avoided because the rearrangement of 4-alkoxypyridines to *N*-alkyl-4-pyridones began from 150°C on. However, over ruthenium dioxide in methanol–water, the hydrogenation of 4-alkoxypyridines to the corresponding piperidines proceeded at 135–140°C, as shown in eq. 12.33 for 4-methoxypyridine, and thus the formation of the *N*-alkylpyridones could be depressed.[51]



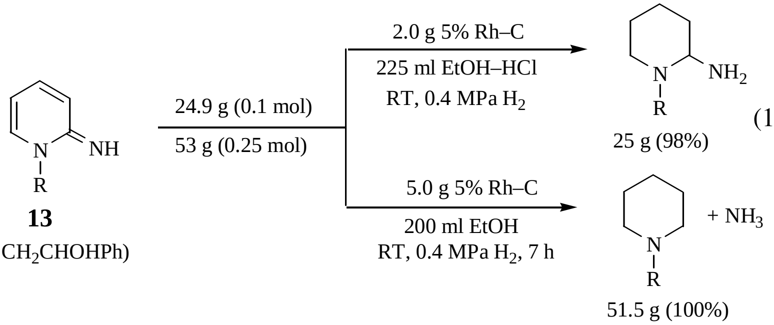
(12.33)

12.1.3.4 Aminopyridines. 2-Aminopyridine, similarly as in 2-hydroxypyridine, may react in its tautomeric structure, 2-imino-1,2-dihydropyridine. The hydrogenation of 2-aminopyridine with colloidal platinum (Skita) in aqueous solution containing excess hydrochloric acid or with platinum black in the presence of excess hydrochloric acid in aqueous or alcoholic solution led to quantitative formation of 2-iminopiperidine hydrochloride with absorption of 2 equiv of hydrogen.[49] When 2-aminopyridine hydrochloride was hydrogenated over Adams platinum oxide in neutral aqueous solution, 4 equiv of hydrogen was absorbed with formation of ammonia and piperidine (Scheme 12.7). When 2-iminopiperidine hydrochloride was hydrogenated with platinum black in neutral aqueous solution, no absorption of hydrogen took place, while with platinum oxide the hydrogenation proceeded but the product was again ammonia and piperidine even with uptake of about 1 equiv of hydrogen. Such hydrogenolysis or deamination, however, could be avoided in the hydrogenation of 1-alkyl-2-imino-1,2-dihydropyridine **13** as a hydrochloride over 5%



Scheme 12.7 Hydrogenation of 2-aminopyridine over platinum catalysts.

Rh–C in ethanol.[52] Hydrogenation with the free base led to quantitative hydrogenolysis to give 1-alkylpiperidine and ammonia (eq. 12.34).

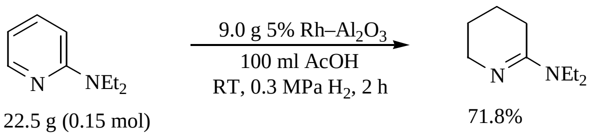


13

(R = CH$_2$CHOHPh)

(12.34)

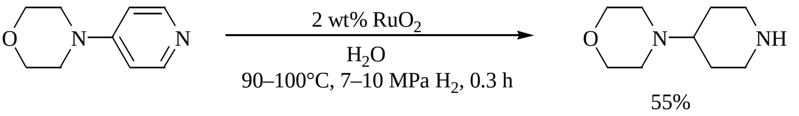
Pyridines with a secondary or tertiary amino group on the 2 position are hydrogenated to 3,4,5,6-tetrahydropyridines with absorption of 2 mol of hydrogen. For example, hydrogenation of 2-benzylaminopyridine gave the corresponding 3,4,5,6-tetrahydropyridine over palladium oxide in acetic acid.[53] 2-Methylamino- and 2-diethylaminopyridines (eq. 12.35) were also hydrogenated to the corresponding 3,4,5,6-tetrahydropyridines over 5% Rh–Al_2O_3.[54] These results might be expected because the N=C bond of the –N=C–N < moiety in an amidine is known to be rather resistant to hydrogenation.[55]



(12.35)

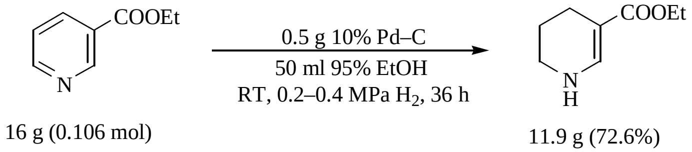
3-Aminopyridine behaves like an aromatic amine and has been hydrogenated without difficulty over platinum oxide in dilute hydrochloric acid to give 3-aminopiperidine dihydrochloride.[56] 4-Aminopyridine was hydrogenated only very slowly over plati-

num oxide in alcoholic hydrogen chloride at 0.8 MPa H_2 and afforded only 16.5% of 4-aminopiperidine dihydrochloride.[57] On the other hand, 4-morpholinopyridine, a 4-tertiary amino pyridine, was readily hydrogenated over ruthenium dioxide in water at an elevated temperature and pressure (eq. 12.36).[27]



(12.36)

12.1.3.5 Partial Hydrogenation to Tetrahydropyridines. Pyridines with a carbonyl function such as COR, COOR, or $CONH_2$ at the 3 position can be hydrogenated to the corresponding 1,4,5,6-tetrahydropyridines over palladium catalyst under mild conditions.[58–61] Thus, ethyl nicotinate and nicotinamide were hydrogenated to the corresponding tetrahydro derivatives in some 70% yields (eqs. 12.37 and 12.38).[60] The small amounts of the corresponding piperidines isolated were considered not to arise from further hydrogenation of the tetrahydro products, since the reactions were allowed to proceed until no hydrogen absorption was observable.



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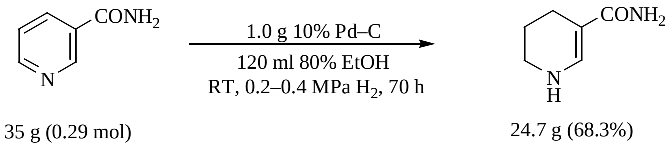
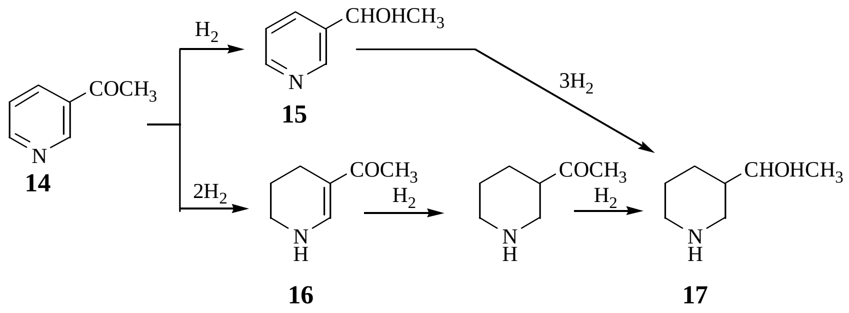


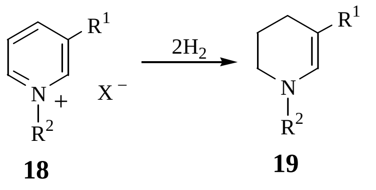
(12.38)

Freifelder studied the hydrogenation of isomeric acetylpyridines with noble metal catalysts.[58] 3-Acetylpyridine (**14**) was hydrogenated to 3-acety-1,4,5,6-tetrahydropyridine (**16**), rather than to 3-(1-hydroxyethyl)pyridine (**15**), in a 70% yield over Pd–C in ethanol at room temperature and 0.3 MPa H_2 when uptake of hydrogen was allowed to continue until it stopped. Later it was found that **16** could not be hydrogenated further with palladium catalyst in neutral or acidic solution.[62] In contrast, 2- and 4-acetylpyridines were hydrogenated to the corresponding (1-hydroxyethyl)pyridines as major products. With Rh–Al_2O_3 as catalyst, the major product from **14** was 3-(1-hydroxyethyl)piperidine (**17**) when the hydrogenation was allowed to continue until uptake of hydrogen stopped. Compound **17** was probably formed via **16** as the major intermediate, since 33% of **16** and only 9% of **15** were found in the product, together with 58% of the starting pyridine, when the hydrogenation was stopped after 1 equiv of hydrogen had been absorbed. Over platinum oxide, however, the hydrogenation to

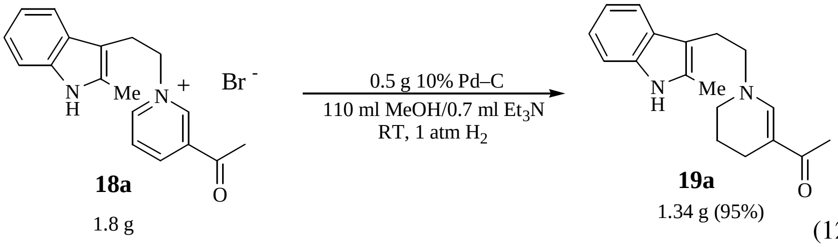


Scheme 12.8 Hydrogenation pathways of 3-acetylpyridine.

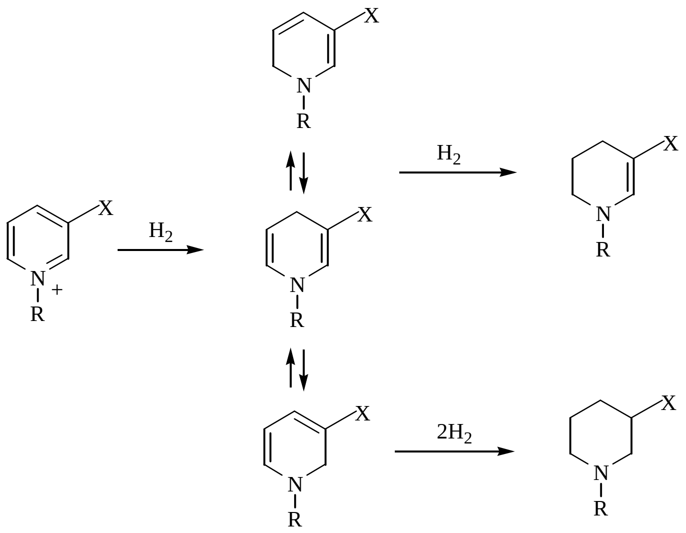
15 appears to be the major pathway leading to the formation of **17**, since 75% of **15** was formed together with 21% of **16** at the uptake of 1.25 equiv of hydrogen (Scheme 12.8).[58] A number of 1-substituted pyridinium salts with an electron-withdrawing unsaturated group on the 3 position have also been hydrogenated to the corresponding 1,4,5,6-tetrahydropyridines over palladium catalyst.[61,63–65] Wenkert et al. transformed compounds **18a–18k** into the corresponding 1,4,5,6-tetrahydropyridines **19a–19k** in good yields over Pd–C in methanol in the presence of triethylamine at room temperature and atmospheric pressure.[61,63] An example with the compound **18a** is shown in eq. 12.39.



a: R^1 = Ac; R^2 = β-[3-(2-methylindolyl)]ethyl
b: R^1 = CHO; R^2 = β-[3-(2-methylindolyl)]ethyl
c: R^1 = CO_2Me; R^2 = β-[3-(2-methylindolyl)]ethyl
d: R^1 = CO_2Bu^t; R^2 = β-[3-(2-methylindolyl)]ethyl
e: R^1 = Ac; R^2 = $(CH_2)_2OH$
f: R^1 = Ac; R^2 = CH_2OMe
g: R^1 = $COCH_2CO_2Me$; R^2 = Me
h: R^1 = Ac; R^2 = Me
i: R^1 = CO_2Me; R^2 = Me
j: R^1 = $CONH_2$; R^2 = Me
k: R^1 = CN; R^2 = Me

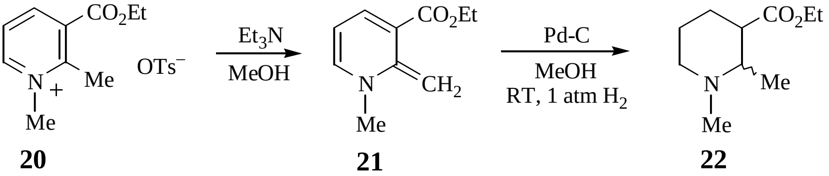


(12.39)



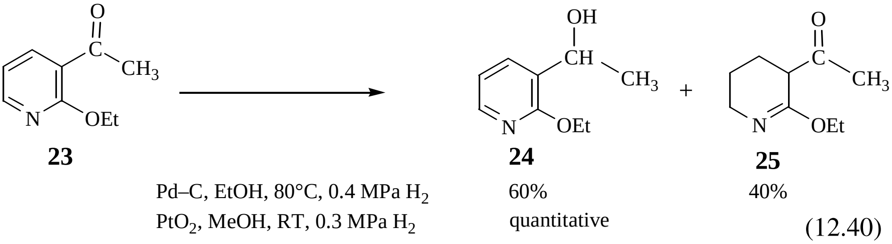
Scheme 12.9 Probable hydrogenation pathways of the pyridinium salt having an electron-withdrawing group at the 3 position.

The resistance to hydrogenation of 1,4,5,6-tetrahydropyridines with a carbonyl function on the 3 position has been explained by their structure stabilized as a vinylogous amide system, which is characterized by the carbonyl stretching absorption in the infrared at much lower frequencies than would be expected for simple unsaturated ketones and the intense ultraviolet absorption near 300 nm.[58,60] Since 1,2-, 1,4-, and 1,6-dihydro isomers derived from 1-alkyl-3-cyanopyridines are all hydrogenated to give 1,4,5,6-tetrahydropyridines, Lyle and Mallet have suggested that an equilibrium between these isomers may exist on the catalyst surface prior to further hydrogenation and that the structure of the product is then determined by which of these isomeric dihydropyridines undergoes hydrogenation in the greatest rate (see Scheme 12.9),[65] although the 1,4 isomer has been shown to be the most stable isomer,[66] and the hydrogenation of this isomer appears to be the most probable pathway leading to the formation of 1,4,5,6-tetrahydropyridines.[58] Some unusual results on the partial hydrogenation described above have been obtained with 2-substituted pyridine derivatives. The hydrogenation of 2-methylpyridinium salt **20** produced the piperidine **22** exclusively, instead of forming the corresponding 1,4,5,6-tetrahydropyridine, over Pd–C in methanol in the presence of triethylamine under ordinary conditions.[61] This unusual result was explained by assuming that prior to hydrogenation the base had converted **20** at least partly into compound **21**, which then underwent hydrogenation to give **22** (Scheme 12.10). The presence of **21** was supported by the formation of a deep red color on addition of triethylamine to the alcohol solution of **20**. The hydrogenation of 2-ethoxy-3-acetylpyridine (**23**) with palladium catalyst afforded 60% of 2-ethoxy-3-(1-hydroxyethyl)pyridine (**24**) and 40% of the 3,4,5,6-tetrahydro derivative **25** in ethanol at 80°C and 0.4 MPa H_2. In the hydrogenation with platinum oxide in metha-

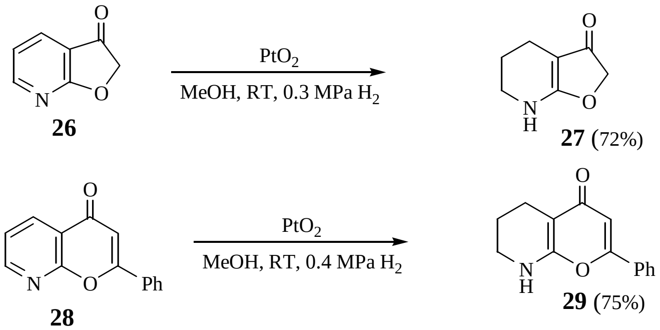


Scheme 12.10 Possible hydrogenation pathway of ethyl 2-methylnicotinate methotosylate over palladium in the presence of triethylamine.

nol at room temperature, **24** was formed quantitatively (eq. 12.40). By contrast, the hydrogenation of the bicyclic compounds **26** and **28** under the same conditions afforded the corresponding 1,4,5,6-tetrahydropyridines **27** and **29** in good yields (eq. 12.41).[67] The different behavior of **23** and the cyclic compounds **26** and **28** toward hydrogenation has been explained by the effects of an internal strain by which a β-keto iminoether structure (**I**, Scheme 12.11) is favored in **25** while an α-alkoxyenamino ketone structure (**II**, Scheme 12.11) is favored in **27** and **29**.[67]



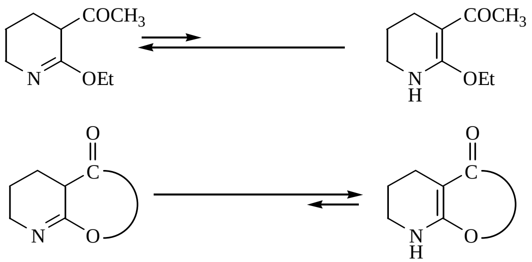
(12.40)



(12.41)

12.1.4 Quinolines, Isoquinolines, and Related Compounds

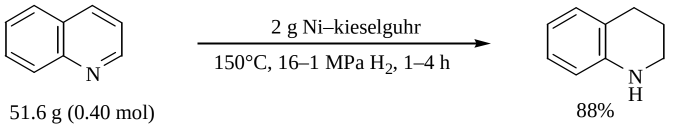
12.1.4.1 Quinolines. Quinoline is usually hydrogenated in its pyridinoid ring first to give 1,2,3,4-tetrahydroquinoline, which is further hydrogenated to give decahydroquinoline under more vigorous conditions and/or in a longer reaction time. Over Ni–kieselguhr at high pressures the pyridinoid ring is rapidly hydrogenated at temperatures from about 125°C upward (eq. 12.42). The hydrogenation to



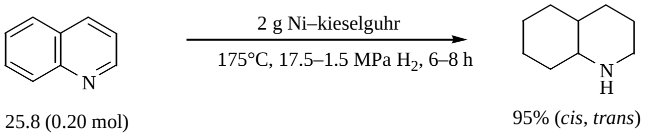
I **II**

Scheme 12.11 Tautomerism in acyclic and cyclic 2-alkoxy-3-acetylpyridines.

decahydroquinoline requires a considerably higher temperature and a longer reaction time with use of a higher catalyst:substrate ratio (eq. 12.43).[1]

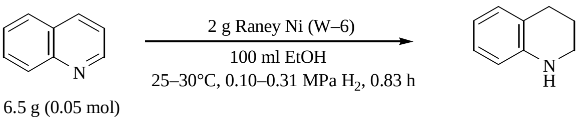


(12.42)



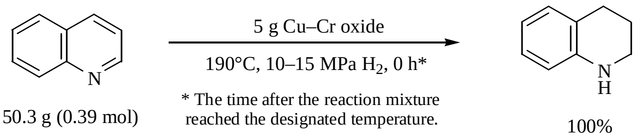
(12.43)

In another example with a reduced nickel catalyst under 7.0 MPa H_2, quinoline was hydrogenated at 70°C to give 1,2,3,4-tetrahydroquinoline, at 100°C to a mixture of 1,2,3,4-tetrahydroquinoline and a small amount of 5,6,7,8-tetrahydroquinoline, and at 210°C to give 62% yield of *trans*-decahydroquinoline and 21% of a mixture consisting of *cis*-decahydroquinoline and 5,6,7,8-tetrahydroquinoline.[68] The hydrogenation of quinoline (52.9 g, 0.41 mol) to decahydroquinoline over Raney Ni (5 g) required 4 h at 200C.[69] Over highly active W-6 Raney Ni, the hydrogenation to tetrahydroquinoline was achieved even at room temperature and 0.10–0.31 MPa H_2 in ethanol (eq. 12.44).[70]



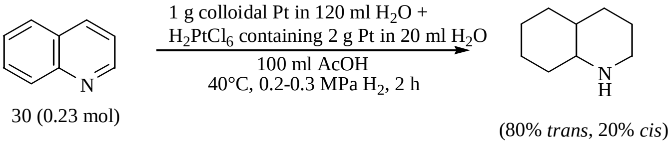
(12.44)

Over copper–chromium oxide, quinoline is quantitatively hydrogenated to tetrahydroquinoline, and further hydrogenation to decahydroquinoline does not proceed even at 190°C and 10–15 MPa H_2 (eq. 12.45).[71] Over reduced copper catalyst quinoline was hydrogenated to tetrahydroquinoline at 130°C and 14 MPa H_2. Hydrogenation of the tetrahydroquinoline produced took place only very slowly at 260°C and 16 MPa H_2 to give *trans*-decahydroquinoline.[20]



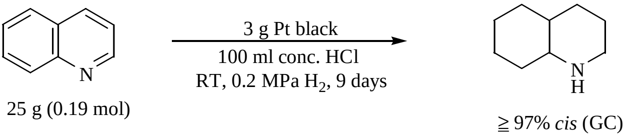
(12.45)

Over ruthenium dioxide quinoline was hydrogenated to tetrahydroquinoline in 97.5% yield at 80°C and 8.2 MPa H_2 and to decahydroquinoline in 98% yield at 120°C and 9.3 MPa H_2.[3] Quinoline was also hydrogenated to tetrahydroquinoline over colloidal platinum in neutral solution[72] or as the hydrochloride over platinum oxide in absolute ethanol.[30] Hydrogenation to decahydroquinoline was performed with platinum black (Willstätter) or colloidal platinum (Skita) in acetic acid.[73,74] Hückel and Stepf hydrogenated quinoline under almost the same conditions as used by Skita and Meyer, and obtained the decahydroquinoline consisting of approximately 80% of *trans* and 20% of *cis* isomers (eq. 12.46).



(12.46)

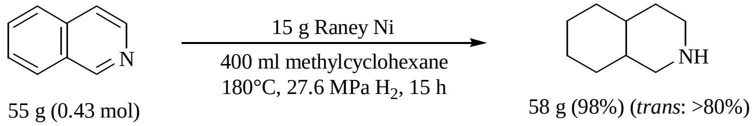
Formation of the *cis* isomer increased to 65% when quinoline was hydrogenated in acetic acid added by a large quantity of hydrochloric acid.[72] Booth and Bostock obtained practically pure *cis*-decahydroquinoline by hydrogenation of quinoline in concentrated hydrochloric acid over platinum black (eq. 12.47).[75] Vierhapper and Eliel showed that the hydrogenation in the strongly acidic medium proceeds mostly via 5,6,7,8-tetrahydroquinoline as intermediate, which probably is related to the high stereoselectivity in the formation of the *cis* isomer.[37]



(12.47)

12.1.4.2 Isoquinolines. Similarly to hydrogenation with quinoline, hydrogenation of isoquinoline usually occurs at the nitrogen ring first to give 1,2,3,4-tetrahydroisoquinoline. However, over colloidal platinum further hydrogenation to decahydroisoquinoline appears much more difficult than in the case of quinoline.[76,77] Thus under the conditions at which quinoline was hydrogenated to decahydroquinoline, isoquinoline was not hydrogenated beyond the tetrahydro stage.[77] This may be compared to the situation that hydrogenation of the benzenoid ring is more difficult in benzylamine and 2-phenylethylamine than in aniline.[77,78] Skita effectuated the transformation of isoquinoline to decahydroisoquinoline by hydrogenating 10 g of isoquinoline first to tetrahydroisoquinoline over the catalyst from chloroplatinic acid solution containing 1.5 g of platinum and colloidal platinum

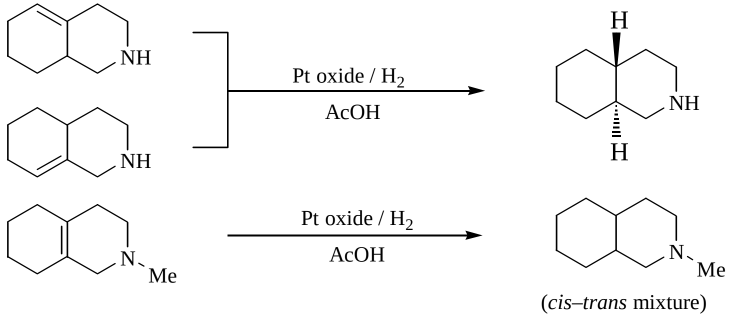
solution containing 0.05 g of platinum at 50–60°C and 0.3 MPa H_2 in 40 ml of acetic acid and 10 ml of concentrated hydrochloric acid. The theoretical amount of hydrogen corresponding to 2 mol had been absorbed in 2.8 h, and then the hydrogenation was resumed with the addition of chloroplatinic acid containing 2.4 g of platinum at 55–60°C and 0.3 MPa H_2 for 11 h.[77] Thus the total time required for hydrogenation to decahydroisoquinoline was about 14 h, even with use of ~40 wt% of platinum to the substrate. Witkop hydrogenated 1 g of isoquinoline over 1 g of platinum oxide in acetic acid with a small amount of sulfuric acid at room temperature and atmospheric pressure and obtained the decahydroisoquinoline containing 70–80% of the *cis* isomer and 20% of the *trans* isomer.[79] Witkop also hydrogenated isoquinoline using Raney Ni in almost quantitative yield to a mixture of *cis*- and *trans*-decahydroisoquinolines containing at least 80% of the *trans* isomer (eq. 12.48).[80]



(12.48)

In relation to the hydrogenation stereochemistry of isoquinoline, it is of interest to note that a mixture of isomeric octahydroisoquinoline, most likely $\Delta^{5,10}$ and $\Delta^{8,9}$ isomers, which is obtained by reduction of isoquinoline or tetrahydroisoquinoline with lithium in either propylamine or ethylenediamine, gives almost pure *trans*-decahydroisoquinoline on hydrogenation over platinum oxide in acetic acid. On the other hand, *N*-methyl-$\Delta^{9,10}$-octahydroisoquinoline, obtained similarly by reduction of *N*-methyltetrahydroisoquinoline, gives a mixture of *cis*- and *trans*-decahydroisoquinolines (Scheme 12.12).[81]

12.1.4.3 Selectivity to Tetrahydro Derivatives. As already described, the hydrogenation of quinoline and isoquinoline usually occurs at the nitrogen ring to give the corresponding 1,2,3,4-tetrahydro derivatives, unless bulky substituents in the 2, 3,



Scheme 12.12 The stereochemistry of hydrogenation of octahydroisoquinolines over platinum.

and 4 positions prevent the hydrogenation of the nitrogen ring, as observed with some alkyl-substituted quinolines. Von Braun et al. studied the influence of alkyl substituents on the formation of 1,2,3,4- or 5,6,7,8-tetrahydroquinolines over an unsupported nickel catalyst at about 200°C and 2 MPa H_2.[82] In general, hydrogenation of either ring becomes increasingly difficult with increasing alkyl substitution in its ring. The bulkiness and position of a substituent may also influence the selectivity. Thus the proportion of hydrogenation in the benzene ring for substituted quinolines (see figures in parentheses) increased in the following order: 2,6-dimethyl (1.5) < 2,4,5,8-tetramethyl (4), 2-methyl (4) < 4-methyl (33) < 2-propyl (35) < 2,3-dimethyl (44) < 2,4-dimethyl (80) < 4-phenyl-2-methyl (84) < 2,3,4-trimethyl (100), while with 6-, 7-, and 8-methylquinolines the hydrogenation in the pyridine ring occurred quantitatively.[82]

Shaw and Stapp studied the selectivity of various transition metal catalysts in the hydrogenation of methyl-substituted quinolines in hexadecane mostly at 100–160°C and an initial hydrogen pressure of 5.17 MPa (at room temperature).[15] As seen from the results shown in Table 12.4, with 2-methylquinoline the selectivity to 1,2,3,4-

TABLE 12.4 Selectivities of Transition Metals in the Hydrogenation of Methyl-Substituted Quinolines to Tetrahydroquinolines[a,b]

Quinoline	Catalyst[c]	Temperature (°C)	Time (h)[d]	Product Ratio (%)[e] 1,2,3,4-Tetrahydro	Product Ratio (%)[e] 5,6,7,8-Tetrahydro
2-Methyl	$Pd–Al_2O_3$	160	1.0	54	46
2-Methyl	$Pt–Al_2O_3$	150	1.0	92[f]	8[f]
2-Methyl	Pt–C	150	1.0	96[f]	4[f]
2-Methyl	$Ru–Al_2O_3$	160	1.6	74[g]	26[g]
2-Methyl	$Rh–Al_2O_3$	100	0.5	63	37
2-Methyl	$Ni–SiO_2–Al_2O_3$	160	1.5	74	26
2-Methyl	Raney Ni	160	2.2	63	37
2-Methyl	$NiO–MoO_3–Al_2O_3$	300	3.0	92[h,i]	8[h,i]
4-Methyl	$Pt–Al_2O_3$	160	2.0	97	3
4-Methyl	$Ni–SiO_2–Al_2O_3$	160	1.5	64	36
6-Methyl	$Pd–Al_2O_3$	105	1.0	98.5	1.5
2,4-Dimethyl	$Pt–Al_2O_3$	160	1.5	88	12

[a]Data of Shaw, J. E.; Stapp, P. R. *J. Heterocycl. Chem.* **1987**, *24*, 1477. Reprinted with permission from the Journal of Heterocyclic Chemistry.
[b]Solvent, hexadecane; initial hydrogen pressure, 5.17 MPa at room temperature. In a typical run 10 g (0.070 mol) of 2-methylquinoline was hydrogenated in 90 g of hexadecane over 0.20 g of 5% $Pt–Al_2O_3$. The amounts of catalyst were 0.70, 1.0, and 1.0 g for $Ni–SiO_2–Al_2O_3$, Raney Ni, and $NiO–MoO_3–Al_2O_3$, respectively, instead of the usual 0.20 g.
[c]All catalysts are 5% metal except for $Ni–SiO_2–Al_2O_3$, which is 60–65% Ni and $NiO–MoO_3–Al_2O_3$, which is 2.7% Ni (as NiO) and 13.2% Mo (as MoO_3).
[d]An additional 0.5 h was needed to reach the desired temperature.
[e]Unless otherwise specified, no other products were observed except for 2–3% starting material.
[f]Absolute yield of two products totaled 100%.
[g]Decahydroquinolines were also produced (12% of products).
[h]In this case 6–7% starting material was unreacted.
[i]At 250°C the ratio was 99:1.

tetrahydro compound increased with respect to the catalyst in the following order: Pd–Al_2O_3 < Raney Ni=Rh–Al_2O_3 < Ru–Al_2O_3=Ni–SiO_2–Al_2O_3 < Pt–Al_2O_3=NiO–MoO_3–Al_2O_3 (at 300°C) < Pt–C < NiO–MoO_3–Al_2O_3 (at 250°C).

When trace amounts of hydrogen sulfide or carbon disulfide were added to the reaction mixture, complete selectivity to 1,2,3,4-tetrahydro compounds has been achieved in the hydrogenation of 2-methyl-, 4-methyl- or 2,4-dimethylquinolines over palladium, platinum, rhodium, ruthenium, or nickel catalyst (Table 12.5). Carbon disulfide was converted to hydrogen sulfide under the hydrogenation conditions. The presence of carbon monoxide was also effective for Pd–Al_2O_3. The absolute yields were 99–100%, based on consumed starting material; the amount of quinoline not hydrogenated was only 2–3%. Thus the sulfur compounds appear to deactivate the catalysts for the hydrogenation of the benzene ring much more than for the pyridine ring. The 1,2,3,4-tetrahydro compounds have also been formed exclusively in the hydrogenation over rhenium, iridium, molybdenum, tungsten, chromium, iron, cobalt–molybdenum, and copper–chromium catalysts without any additive (Table 12.6).

While hydrogenation of quinolines with 2-CO_2Et,[83] 3-CO_2Me,[83] 3-CONEt_2,[84] and 3-CO_2Na[84] groups gives the corresponding 1,2,3,4-tetrahydro derivatives, 4-amino-, 4-hydroxy- and 4-methoxyquinolines were hydrogenated to the 5,6,7,8-tetrahydro de-

TABLE 12.5 Selective Hydrogenation of Methyl-Substituted Quinolines to 1,2,3,4-Tetrahydroquinolines in the Presence of Sulfur Compounds or Carbon Monoxide[a,b]

					Product Ratio (%)[d]	
Quinoline	Catalyst	Additive	Temperature (°C)	Time (h)[c]	1,2,3,4-Tetrahydro	5,6,7,8-Tetrahydro
2-Methyl	Pd–Al_2O_3	CS_2	160	3.3	100[e]	0
2-Methyl	Pd–Al_2O_3	CO[f]	182	2.2	100	0
2-Methyl	Pt–Al_2O_3	H_2S	160	1.5	100	0
2-Methyl	Pt–Al_2O_3	CS_2	160	1.2	100[e]	0
2-Methyl	Ru–Al_2O_3	CS_2	160	3.2	100[g]	0
2-Methyl	Rh–Al_2O_3	CS_2	150	4.2	100[e]	0
2-Methyl	Ni–SiO_2–Al_2O_3	CS_2	175	2.5	100[e]	0
4-Methyl	Pt–Al_2O_3	H_2S	160	2.5	100	0
2,4-Dimethyl	Pt–Al_2O_3	CS_2	160	1.7	100	0

[a]Data of Shaw, J. E.; Stapp, P. R. *J. Heterocycl. Chem.* **1987**, *24*, 1477. Reprinted with permission from the Journal of Heterocyclic Chemistry.

[b]In a typical run 10 g (0.070 mol) 2-methylquinoline was hydrogenated in 90 g of hexadecane over 0.20 g of 5% Pt–Al_2O_3 with addition of 20 μl (0.025 g) of carbon disulfide. With Ni–SiO_2–Al_2O_3 the amount of catalyst was 0.70 g and carbon disulfide was 60 μl (0.075 g). For the other reaction conditions, see footnote *b*, Table 12.4.

[c]See footnote *d*, Table 12.4.

[d]See footnote *e*, Table 12.4.

[e]Absolute yield of product(s) was 99–100%.

[f]A 300-ml autoclave containing the reaction mixture was pressurized to 0.34 MPa with carbon monoxide and then to 5.5 MPa with hydrogen at room temperature.

[g]No decahydroquinoline was present (see footnote *g*, Table 12.4).

TABLE 12.6 Selective Hydrogenation of Methyl-Substituted Quinolines to 1,2,3,4-Tetrahydroquinolines over Re, Ir, Mo, W, Cr, and Fe Catalysts[a,b]

Quinoline	Catalyst (g)[c]	Temperature (°C)	Time (h)[d]	Product Ratio (%)[e] 1,2,3,4-Tetrahydro	5,6,7,8-Tetrahydro
2-Methyl	$Re–Al_2O_3$ (0.2)	171	3.5	100[f]	0
2-Methyl	Ir–C (0.2)	132	2.5	100[f]	0
2-Methyl	IrO_2 (0.3)	150	7	100	0
2-Methyl	$MoO_3–Al_2O_3$ (0.7)	250	5	100[f]	0
2-Methyl	$WO_3–Al_2O_3$ (0.7)	250	3.5	100[f]	0
2-Methyl	$Cr_2O_3–Al_2O_3$ (0.7)	250	3.5	100[f]	0
2-Methyl	$Fe_2O_3–Al_2O_3$ (1.0)	300	7	100[g]	0
2-Methyl	$CoO–MoO_3–Al_2O_3$ (0.7)	250	3	100	0
2-Methyl	Cu–Cr oxide (0.7)	200	3	100	0
2-Methyl	$Fe(CO)_5$ (0.9)	250	7.5	100[g]	0
4-Methyl	$Ir–Al_2O_3$ (0.3)	160	4.5	100	0
2-Isobutyl	$Re–Al_2O_3$ (0.2)	200	7	100	0

[a]Data of Shaw, J. E.; Stapp, P. R. *J. Heterocycl. Chem.* **1987**, *24*, 1477. Reprinted with permission from the Journal of Heterocyclic Chemistry.
[b]See footnote *b*, Table 12.4.
[c]The supported catalysts contained 5% Re, 5% Ir, 10% MoO_3, 10% WO_3, 15% Cr_2O_3, or 20% Fe_2O_3. The $CoO–MoO_3–Al_2O_3$ contained 2.4% Co (as CoO) and 9.8% Mo (as MoO_3).
[d]See footnote *d*, Table 12.4.
[e]See footnote *e*, Table 12.4.
[f]Absolute yield was 99–100% on the basis of consumed starting material.
[g]Unreacted starting material was 20–30%.

rivatives as major products over nickel from nickel formate or Raney nickel as catalyst, respectively, with 4-nitro-, 4-hydroxy-, and 4-methoxyquinoline *N*-oxides as starting materials.[85] 4-Aminoisoquinoline was also hydrogenated to the 5,6,7,8-tetrahydro derivative in 78% yield over platinum oxide in acetic acid with a few drops of concentrated sulfuric acid.[86] Similarly, 1-hydroxy- and 1-alkoxyisoquinolines were hydrogenated to the corresponding 5,6,7,8-tetrahydroisoquinolines in acetic acid without the addition of sulfuric acid, although the yields of the tetrahydro compounds were lower than in the case of 4-aminoisoquinoline.[87]

Hydrogenation in strongly acidic media has been shown to increase the selectivity for preferential hydrogenation at the benzene ring of quinolines, isoquinoline, and phenyl- or phenylalkyl-substituted pyridines.[37,88–90] Results on the hydrogenation of quinolines and isoquinoline over platinum oxide are summarized in Table 12.7. Reaction times were rather long in concentrated hydrochloric acid. However, Vierhapper and Eliel have found that hydrogenation of the benzene ring may be completed in quite short times in trifluoroacetic acid.[37] The yields of 5,6,7,8-tetrahydroquinolines were highest with quinolines having a methyl substituent in the pyridine ring, and lower for quinolines with a methyl substituent in the benzene ring, particularly in the case of 8-methylquinoline. Hönel and Vierhapper studied the selectivity in the hydrogenation

TABLE 12.7 Selective Hydrogenation of Quinolines and Isoquinoline in the Benzene Ring over Platinum Oxide Catalyst

					Product (-Quinoline or -Isoquinoline) (%)			
Compound	Solvent	*T* (°C)	H_2 *P* (MPa)	Time (h)	5,6,7,8-Tetrahydro	1,2,3,4-Tetrahydro	Others	Ref.
Quinoline	Anhydrous MeOH	RT	0.27	35[a]	3	94.5	Decahydro (2.5)	37
	HCl/MeOH (4*M*)	RT	0.1	~7.5[b]	52	39	—	89
	Conc. HCl	RT	0.34	30[c]	70	—	$\Delta^{1,9}$-Octahydro (6) Decahydro (mostly *cis*) (24)	37
	12*N* H_2SO_4	RT	0.34	4.5[c]	74	13	$\Delta^{1,9}$-Octahydro(6.5) Decahydro (5.5)	37
	CF_3CO_2H	RT	0.34	0.75[c]	84	4.5	$\Delta^{1,9}$-Octahydro (5) Decahydro (3) Unidentified (3.5)	37
	Liq. HF	25	0.11	1.5[d]	75	8	Starting material (17)	90
	Liq. HF	25	0.11	17[d]	50	—	Decahydro (50)	90
2-Me	CF_3CO_2H	RT	0.34	0.75–1.5[c]	95	—	Not isolated (5)	37
2-*i*-Pr	CF_3CO_2H	RT	0.34	0.75–1.5[c]	95	—	Not isolated (5)	37
6-Me	CF_3CO_2H	RT	0.34	0.75–1.5[c]	74[e]	18.7	$\Delta^{1,9}$-Octahydro (3.3) Decahydro (2.1) Starting material (1.8)	37
8-Me	CF_3CO_2H	RT	0.34	0.75–1.5[c]	55.8[e]	27.2	$\Delta^{1,9}$-Octahydro (8.1) Decahydro (1.8) Starting material (7.1)	37

TABLE 12.7 Continued

Compound	Solvent	T (°C)	H_2 P (MPa)	Time (h)	Product (-Quinoline or -Isoquinoline) (%)			Ref.
					5,6,7,8-Tetrahydro	1,2,3,4-Tetrahydro	Others	
Isoquinoline	AcOH	RT	0.1	4.5[f]	5.8	61.9	*c*-Decahydro (20.8) *t*-Decahydro (7.7) Unidentified (3.8)	37
	AcOH	RT	0.1	35[g]	—	—	*c*-Decahydro (62.5) *t*-Decahydro (33.2) Unidentified (4.3)	37
	HCl/MeOH (4*M*)	RT	0.1	~2.7[b]	87	13	—	89
	$AcOH/H_2SO_4$ (10 ml per 5 drops)	RT	0.1	3[f]	80	8.3	Decahydro (1.8) Starting material (7.9) Unidentified (2)	37
	Conc. HCl	RT	0.34	—[c]	95	—	Not isolated (5)	37
	CF_3CO_2H	RT	0.1	16[h]	90.5	1.5	Decahydro (4) Unidentified (4)	37
	Liq. HF	25	34.5	18[i]	66	—	66% conversion	90

[a]Quinoline (6.45 g, 0.05 mol) was hydrogenated over 0.2 g of PtO_2 in 200 ml of anhydrous methanol at room temperature and a maximum hydrogen pressure of 0.28 MPa until hydrogen uptake had practically ceased.
[b]Quinoline or isoquinoline in 0.25*M* methanol solution was hydrogenated with a 1:10 Pt oxide:substrate ratio at room temperature and atmospheric pressure until approximately 2 equiv of hydrogen had been absorbed.
[c]Quinoline (6.45 g, 0.05 mol) was hydrogenated over 0.75 g of PtO_2 in 40 ml solvent until the required amount of hydrogen had been consumed.
[d]Quinoline (3 g, 0.023 mol) was hydrogenated over 0.3 g PtO_2 in liquid HF (10–30 times the volume of substrate).
[e]Yields of 53 and 55%, respectively, for 6- and 8-methylquinolines were obtained in hydrogenation in concentrated HCl.
[f]Isoquinoline (1 g, 0.0078 mol) was hydrogenated over 1 g of PtO_2 in 10 ml solvent until 2 mol of hydrogen has been absorbed.
[g]Isoquinoline was hydrogenated under the conditions of footnote *f* until hydrogen uptake had practically ceased.
[h]Isoquinoline (6.45 g, 0.05 mol) was hydrogenated over 0.75 g of PtO_2 in 40 ml solvent.
[i]Isoquinoline (12.9 g, 0.10 ml) was hydrogenated over 0.6 g of PtO_2 in liquid HF (10–30 times the volume of substrate).

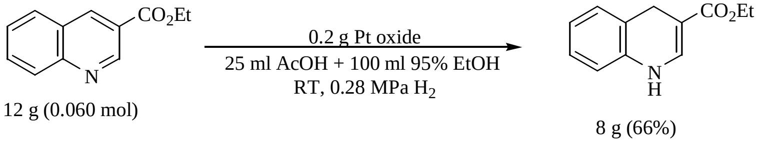
of various 6- and 8-substituted quinolines in trifuoracetic acid.[91] While the methyl substituent in the 6 and 8 positions considerably lowered the selectivity to the product hydrogenated at the benzene ring (from 80% for quinoline to 59 and 51%, respectively), a much higher selectivity—even higher than that for parent quinoline—was obtained with 6- and 8-*t*-butylquinolines (86 and 85%, respectively). Interestingly, a similar effect of bulky alkyl substituents such as *i*-propyl and *t*-butyl has also been observed in the hydrogenation of 1-alkyl-substituted naphthalenes over Pd–C catalyst (see eq. 11.67).[92] *N*-Methyl fluorosulfontates of quinoline, 8-methyl- and 8-*t*-butylquinoline, isoquinoline, and 4-(3-phenylpropyl)pyridine were also hydrogenated over platinum oxide in methanol and in trifluoroacetic acid.[93] Although quaternization of the nitrogen is usually known to facilitate the hydrogenation of the nitrogen ring, similar high selectivity for the hydrogenation of the benzene ring as in the parent pyridine bases was obtained when *N*-methyl quaternary salts were hydrogenated in trifluoroacetic acid, while in methanol the reaction was more facile with the salts than with the parent bases and the products were nearly pure pyridine ring-hydrogenated derivatives.

Okazaki et al. studied the hydrogenation of isoquinoline and quinoline over Raney Ni and supported ruthenium as catalysts and suggested the hydrogenation pathways from a kinetic analysis. When Raney Ni was employed for the hydrogenation of sulfur-free isoquinoline at relatively high temperature and relatively low hydrogen pressure (205–210°C and 1.5–2.5 MPa), 5,6,7,8-tetrahydroisoquinoline and *trans*-decahydroisoquinoline were selectively obtained in 90 and 80% yields, respectively, by adjusting the reaction temperature.[94] In contrast, with sulfur-containing compound, 1,2,3,4-tetrahydroisoquinoline was formed exclusively, and product selectivity varied little within 150–250°C and hydrogen pressures of 1–14 MPa. Hydrogenation of sulfur-containing isoquinoline over Ru–C also gave the 1,2,3,4-tetrahydro compound exclusively.[95] Thus the sulfur compound blocks the hydrogenation of the benzene ring of isoquinoline very effectively (see also Table 12.5). The formation of 5,6,7,8-tetrahydroisoquinoline in high yields with a sulfur-free compound was shown to result from an extensive isomerization of the 1,2,3,4-tetrahydroisoquinoline first formed as the major product to the 5,6,7,8-tetrahydro compound that might occur faster than further hydrogenation of the 1,2,3,4-tetrahydro intermediate to the decahydro compound at a high temperature and low hydrogen pressure. Okazaki et al. have also shown that the isomerization of the initially formed 1,2,3,4-tetrahydroquinoline to 5,6,7,8-tetrahydro derivative occurs similarly in the hydrogenation of quinoline over Raney Ni at about 200°C and 1 MPa H_2, although the reactivity of 1,2,3,4-tetrahydro derivative toward isomerization was lower in quinoline than in isoquinoline.[96] In contrast, in hydrogenation over Ru–C and Ru–Al_2O_3 at 135–170°C and 5–10 MPa H_2, 1,2,3,4-tetrahydroquinoline was hydrogenated to the perhydro derivative with little isomerization to the 5,6,7,8 derivative.[97] It is noted that the amount of 5,6,7,8-tetrahydroisoquinoline formed simultaneously with 1,2,3,4-tetrahydro derivative (the 5,6,7,8-/1,2,3,4- ratio is given in parentheses) is much larger over Ru–Al_2O_3 (0.77 at 150°C) than over Ru–C (0.14 at 150°C). It has been suggested that an acidic nature of the alumina sup-

port deactivated the hydrogenation of the nitrogen ring in isoquinoline. The hydrogenation and isomerization of 1,2,3,4-tetrahydroquinoline over Raney Ni was completely inhibited in the presence of quinoline or isoquinoline.

12.1.4.4 Hydrogenation to Dihydro Derivatives. Similarly to 2-hydroxypyridines, 2-hydroxyquinoline (carbostyril) and 1-hydroxyisoquinoline (isocarbostyril) are hydrogenated to the 3,4-dihydro compounds over palladium black (Willstätter) in ethanol or dioxane at 55°C and 0.1–0.3 MPa H_2 (Scheme 12.13), while 3-, 5-, 6-, 7-, and 8-hydroxyquinolines are hydrogenated to yield the corresponding 1,2,3,4-tetrahydroquinolines.[39] 4-Hydroxy-, 4-hydroxy-2-methyl-, and 2-hydroxy-4-methylquinolines were not hydrogenated under the conditions employed.

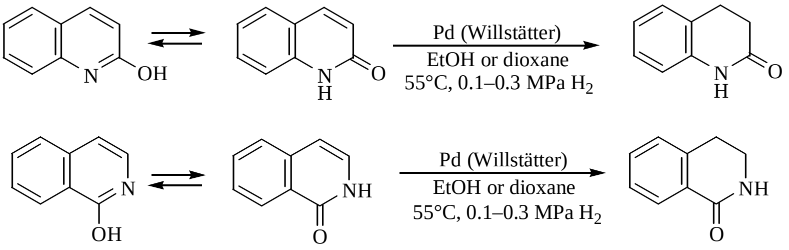
Quinolines with a carbonyl function in the 3 position are often hydrogenated to give the corresponding 1,4-dihydro compounds, which possess a vinylogous amide moiety that may be stable to further hydrogenation, as discussed in the pyridine series (Section 12.1.3.5). Thus the quinolines with 3-acetyl over Raney Ni in ethanol (RT, 1 atm H_2),[98] with 3-methoxycarbonyl over Pd–C in methanol (60–65°C, 9 MPa H_2),[84] and with 3-ethoxycarbonyl over platinum oxide in acetic acid-ethanol (eq. 12.49)[99] were hydrogenated to give the corresponding 1,4-dihydro products.



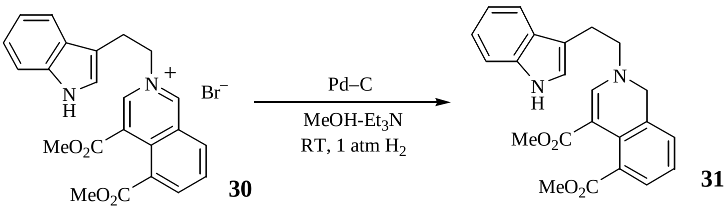
(12.49)

Wenkert et al.[100] hydrogenated the isoquinolinium salt **30** to the dihydro derivative **31**, which also had a stable vinylogous amide moiety (Scheme 12.14) (see also eq. 12.39).

12.1.4.5 Acridine. Acridine is hydrogenated to 9,10-dihydro derivative over Raney Ni at 25°C and over copper–chromium oxide at 150°C in dioxane.[9,101] Over Raney Ni at 100°C, acridine or 9,10-dihydroacridine is hydrogenated to a mixture of *as*- and *s*-octahydro and dodecahydro derivatives. However, over copper–chromium oxide at 190°C, *as*-octahydro derivative is formed in high selectivity, although a small amount of dodecahydro derivative is also formed.[9] The formation of

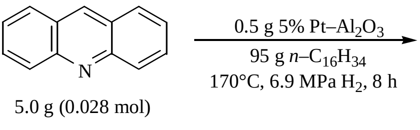


Scheme 12.13 Hydrogenation of 2-hydroxyquinoline and 1-hydroxyisoquinoline to 3,4-dihydro compounds.

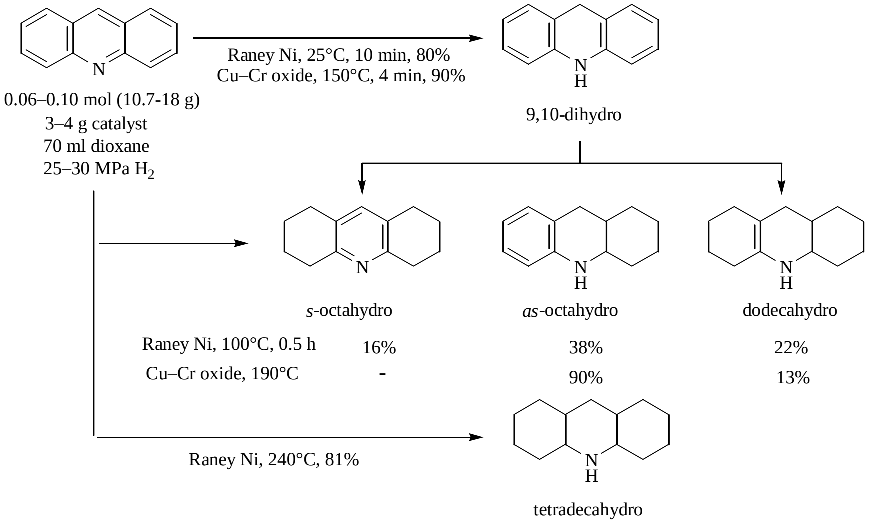


Scheme 12.14 Partial hydrogenation of isoquinolinium salt with 3-methoxycarbonyl group to the dihydro derivative.

s-octahydroacridine from the 9,10-dihydro derivative indicates that the hydrogenation involves the migration of hydrogen or disproportionation reaction, just as in the formation of *s*-octahydrophenanthrene from the 9,10-dihydro derivative. The hydrogenation to perhydroacridine was achieved over Raney Ni at 240°C. The reactions of acridine and 9,10-dihydroacridine over Raney Ni and copper–chromium oxide are summarized in Scheme 12.15. 9,10-Dihydroacridine was also obtained in 98.5% yield from acridine over ruthenium dioxide at 100°C and 9 MPa H_2[3] and in 96% yield over 5% $Pt–Al_2O_3$ (eq. 12.50) or $Re–Al_2O_3$ in hexadecane at 170°C and 6.9 MPa H_2.[15] Over ruthenium dioxide at 180°C and 11 MPa H_2, acridine is hydrogenated to the perhydro derivative.



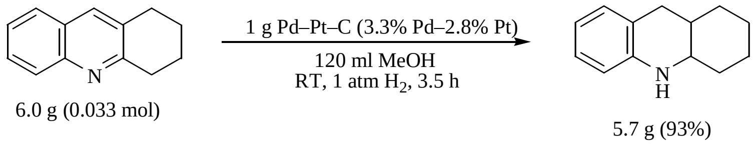
(12.50)



Scheme 12.15 Hydrogenation of acridine and 9,10-dihydroacridine over Raney Ni and Cu–Cr oxide.

Mochida et al. undertook a comparative study on the hydrogenation of acridine over carbon- or alumina-supported platinum metals (Pd, Rh, Pt, Ru) in decalin at 100°C and 6.9 MPa H_2.[102] Palladium and platinum catalysts were found to be selective for producing 9,10-dihydro derivative, while rhodium and ruthenium catalysts exhibited lower selectivity for the dihydro derivative, even at low conversions, and showed a tendency to give various hydrogenation products, even at initial stages of hydrogenation. The highest yields of 9,10-dihydro- and *as*-octahydroacridine (88 and 62%, respectively) was obtained over Pd–Al_2O_3 at 100°C and 6.9 MPa H_2 for 10 min and at 150°C and 13.7 MPa H_2 for 10 min, respectively. The yield of the *as*-octahydro derivative could increase further to 80% first by hydrogenating acridine at 100°C for 10 min and then at 120°C for 60 min. The kinetics and stereochemistry of the hydrogenation of acridine over Pd–Al_2O_3 have been studied under various conditions.[103] By using a kinetic simulation method, the hydrogenation pathway at 150°C was shown to be dominantly a consecutive reaction of acridine → 9,10-dihydroacridine → *as*-octahydroacridine, irrespective of hydrogen pressure. At 250°C, however, the hydrogenation pathways depended on the hydrogen pressure. At 2 MPa H_2, the conversion of 9,10-dihydro to *s*-octahydro via 1,2,3,4-tetrahydro derivative through a hydrogenative isomerization competed with the consecutive hydrogenation of the dihydro to *as*-octahydro derivative. At 7 MPa H_2 the direct pathways of the dihydro to *s*-octahydro and perhydro derivatives were found to contribute to the fast hydrogenation of the dihydro to *as*-octahydro and of *s*-octahydro to perhydro derivatives. At 150°C, the hydrogenation of *as*-octahydro derivative, regardless of the starting *cis*:*trans* ratio, was suggested to proceed preferentially through the isomerization of *cis*-*as*-octahydro to *trans*-*as* isomer, followed by *cis* addition to the latter isomer to form the *trans,syn,cis*–perhydroacridine. At 250°C, the hydrogenation of *as*-octahydro derivative proceeds via isomerization to the more stable *s*-octahydro isomer to produce the most thermodynamically stable *trans,syn,trans*-perhydroacridine.

1,2,3,4-Tetrahydroacridine was hydrogenated to *as*-octahydro derivative in high yield over a Pd–Pt–C catalyst in methanol at ordinary conditions (eq. 12.51).[104] No *s*-octahydroacridine was obtained under the conditions employed. On the other hand, the hydrogenation of acridine over platinum oxide in trifluoroacetic acid leads to quantitative formation of *s*-octahydro derivative (eq. 12.52).[37]



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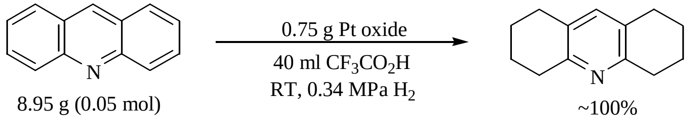
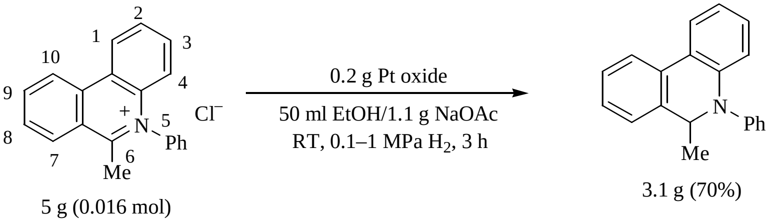


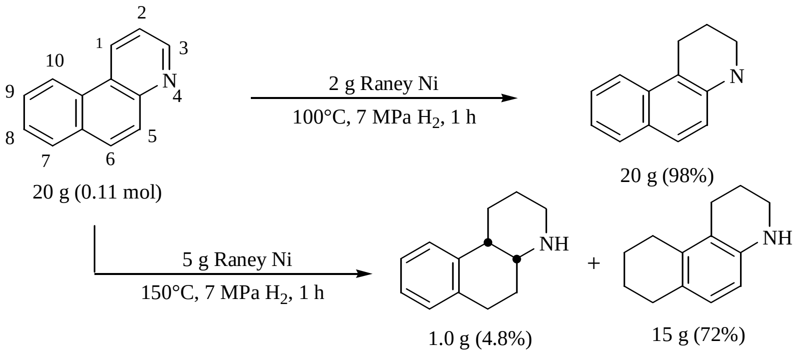
(12.52)

12.1.4.6 Phenanthridine. Phenanthridine is hydrogenated to the 5,6-dihydro derivative quantitatively over Raney Ni at 20°C and 1 atm H_2.[105] Phenanthridinium salts were also hydrogenated to the corresponding 5,6-dihydro derivative over platinum oxide or Pd–C in ethanol with addition of a small amount of sodium acetate (eq. 12.53)[106] or over platinum oxide in ethanolic hydrogen chloride.[107]



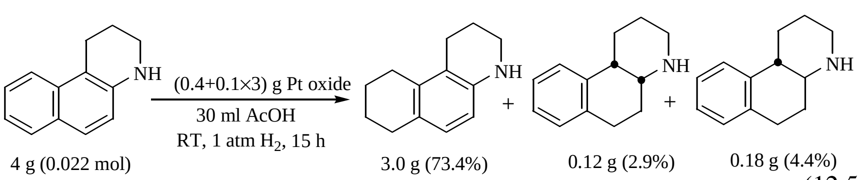
(12.53)

12.1.4.7 Benzo[f]quinoline. Benzo[*f*]quinoline was hydrogenated to the 1,2,3,4-tetrahydro derivative almost quantitatively over Raney Ni at 100°C, while at 150°C a mixture of two octahydro derivatives was produced; a greater part of this mixture was 1,2,3,4,7,8,9,10-octahydro compound (eq. 12.54).[108] No *trans* isomer of 1,2,3,4,4a,5,6,10b-octahydro derivative was isolated.



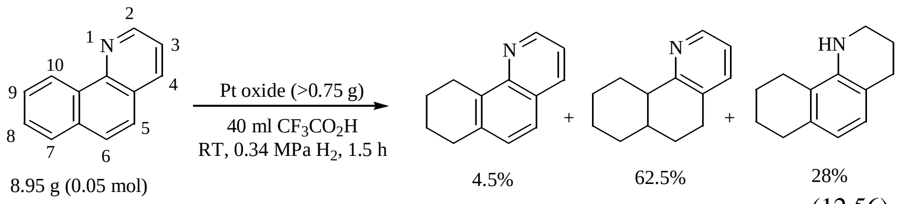
(12.54)

Hydrogenation of 1,2,3,4-tetrahydrobenzo[*f*]quinoline over platinum oxide gave also the 1,2,3,4,7,8,9,10-octahydro compound as the major product together with small amounts of *cis*- and *trans*-1,2,3,4,4a,5,6,10b-octahydro derivative (eq. 12.55). The hydrochloride of the tetrahydro compound was hydrogenated over platinum oxide in ethanol to give the 1,2,3,4,7,8,9,10-octahydro derivative in a better yield of 84% together with 4.5% of *cis*-1,2,3,4,4a,5,6,10b-octahydro compound.[108]



(12.55)

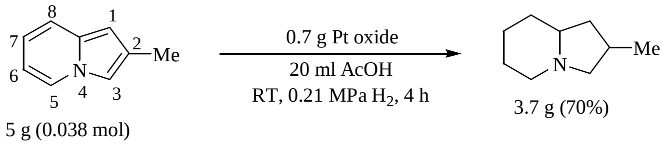
12.1.4.8 Benzo[h]quinoline. In contrast to the case of acridine, the hydrogenation of benzo[*h*]quinoline over platinum oxide in trifluoracetic acid afforded a mixture of two octahydro derivatives together with a small amount of the 7,8,9,10-tetrahydro derivative, although the octahydro compound hydrogenated in the benzene rings was the major product (eq. 12.56).[37]



(12.56)

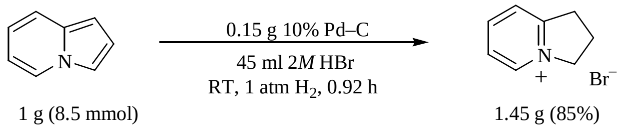
12.1.5 Polynuclear Compounds Containing a Bridgehead Nitrogen

12.1.5.1 Indolizine (pyrrocoline). Indolizine[109,110] and its 2-methyl (eq. 12.57), 3-methyl, and 2,3-dimethyl derivatives[110] were hydrogenated to the corresponding indolizidines (octahydropyrrocolines) over platinum oxide in acetic acid. Indolizine was also hydrogenated to indolizidine over prereduced platinum oxide in ethanol and a drop of hydrochloric acid.[111]



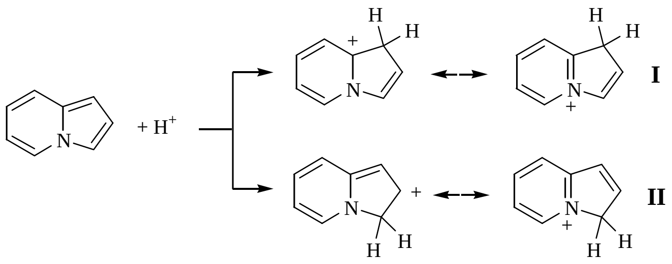
(12.57)

Ochiai and Kobayashi obtained a mixture of 2-methyl-3-ethyl- and 2-methyl-3-α-hydroxyethylindolizidines by the hydrogenation of 3-acetyl-2-methylindolizine over platinum oxide in acetic acid.[112] However, Borrows et al. obtained only small amounts of these compounds in this hydrogenation; the main product was 3-acetyl-2-methyl-5,6,7,8-tetrahydroindolizine, and complete hydrogenation to the perhydro derivatives was best effectuated by using Raney Ni at high temperature and pressure.[113] Indolizine was selectively hydrogenated in the five-membered ring over Pd–C in 2*M* hydrobromic acid solution (eq. 12.58).[114]

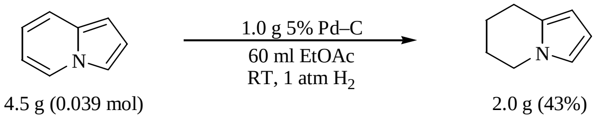


(12.58)

The ease of hydrogenation in the five-membered ring has been explained by the formation of indolizinium ion **I** or **II**, which is a resonance-stabilized pyridinium ion conjugated with an olefinic bond (see Scheme 12.16).[114] On the other hand, it is usual that the hydrogenation of indolizines with Raney Ni,[113,115] copper–chromium oxide,[113] or Pd–C in ethyl acetate (eq. 12.59)[116] leads to the products selectively reduced in the six-membered ring.

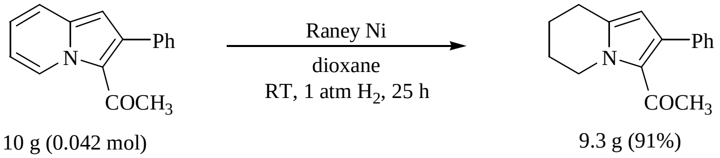


Scheme 12.16 Formation of indolizinium ions by protonation to indolizine.



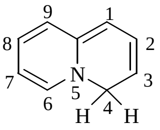
(12.59)

3-Acetyl-2-phenyl- (eq. 12.60) and 3-ethyl-2-phenylindolizines were hydrogenated to the corresponding 5,6,7,8-tetrahydro derivatives over Raney Ni at room temperature.[113] Water and Margolis hydrogenated various 1-substituted 2-phenylindolizines, which were not hydrogenated with palladium or platinum catalysts, over Raney Ni to the 5,6,7,8-tetrahydro derivatives in ethanol at room temperature and 0.41 MPa H_2.[115]

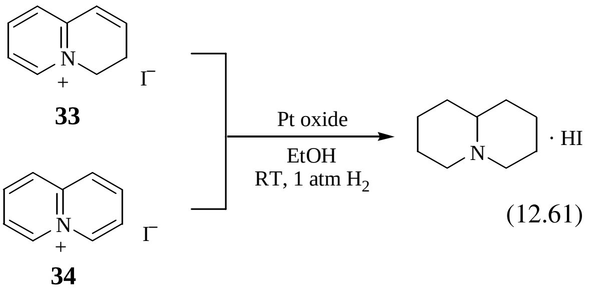


(12.60)

12.1.5.2 Quinolizine (Pyridocoline). Quinolizine (**32**) does not appear to have ever been prepared in a pure state. However, quinolizinium iodide (**33**)[117] and dehydroquinolizinium iodide (**34**)[117,118] were readily hydrogenated over Adams platinum oxide in ethanol to yield quinolizidine hydroiodide with the uptake of 4 and 5 equiv of hydrogen, respectively (eq. 12.61). Similarly, 2-methyldehydroquinolizinium iodide rapidly absorbed 5 mol of hydrogen over platinum oxide in methanol to give octahydro-2-methylquinolizine.[119]

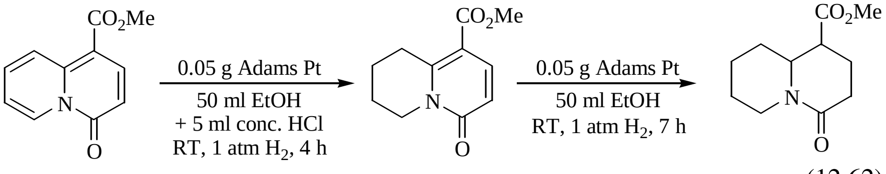


32



(12.61)

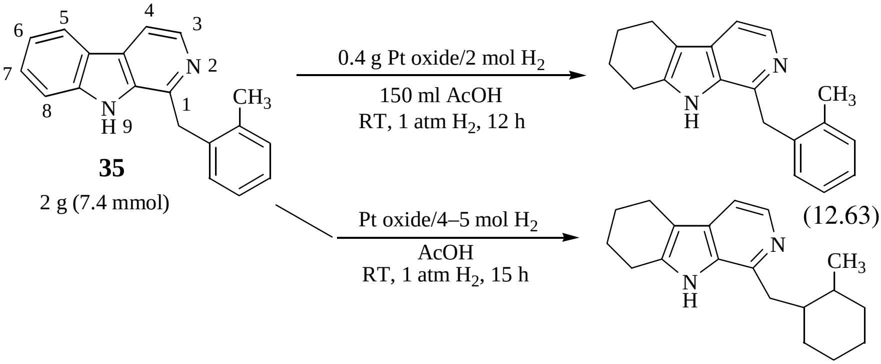
Quinolizones are hydrogenated over platinum oxide with ease to give the corresponding 6,7,8,9-tetrahydro derivatives.[120] It appeared somewhat surprising that the hydrogenation of 1-methoxycarbonyl-4-quinolizone over platinum oxide in acidic medium stopped at the tetrahydro stage and proceeded further only when a neutral medium was employed (eq. 12.62).[121]



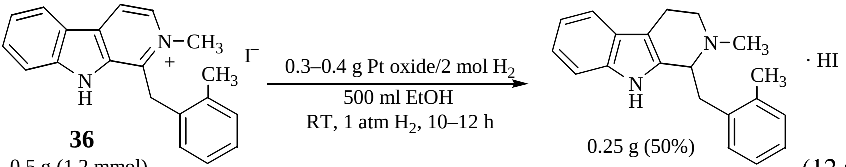
2.0 g (9.9 mmol) 1.6 g (79%) 1.0 g (4.8 mmol) 1.0 g (98%) (12.62)

12.1.6 Polynuclear Compounds with More than One Nitrogen Ring

12.1.6.1 β-Carboline (9H-pyrido[3,4-b]indole). β-Carboline is a common structure that is involved in the harman or carboline alkaloids, and there have been a considerable body of studies on the catalytic hydrogenation of the carboline nucleus. When yobyrine (1-(*o*-methylbenzyl)-β-carboline) (**35**) was hydrogenated over platinum oxide in acetic acid until 2 mol of hydrogen had been absorbed, the 5,6,7,8-tetrahydro derivative was obtained.[122] Hydrogenation for a long period led to the formation of a decahydro compound which was reduced in the benzene rings of the carboline system and the substituent on the 1 position (eq. 12.63).[122,123] On the other hand, the hydrogenation of 2-methylyobyrinium iodide (**36**) over platinum oxide in ethanol gave the product reduced in the pyridine ring (eq. 12.64).[122]

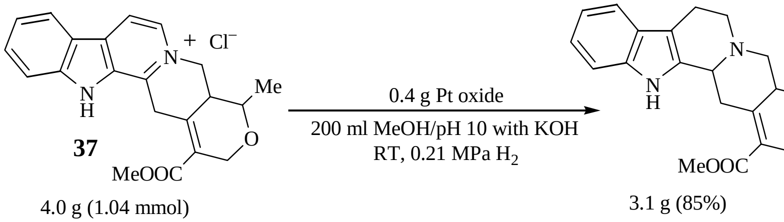


35
2 g (7.4 mmol)
(12.63)

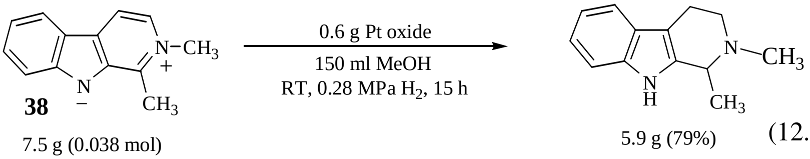


36
0.5 g (1.2 mmol)
0.25 g (50%)
(12.64)

The transformation to the 1,2,3,4-tetrahydro derivatives is best accomplished by hydrogenating the 2-alkyl-β-carboline salts in methanol adjusted to pH 10 with potassium hydroxide, as shown for alstonine hydrochloride (**37**) (eq. 12.65),[124] or hydrogenating the anhydronium base in methanol, as shown with 2-methylharman (**38**) (eq. 12.66).[125]



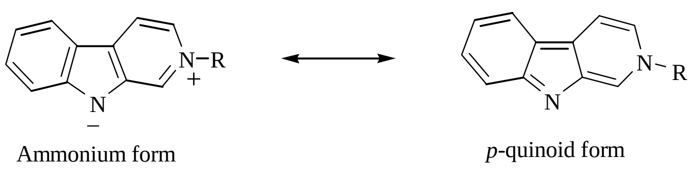
(12.65)



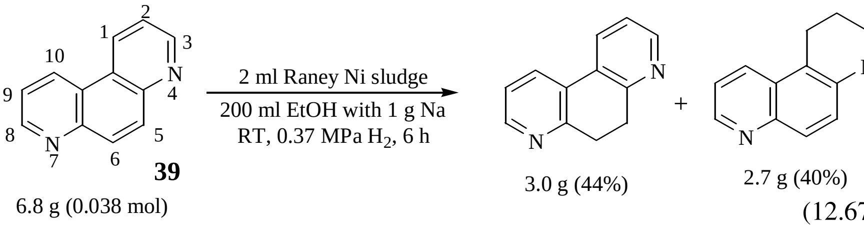
(12.66)

Successful hydrogenation, which occurs only with the anhydronium base (or with the salt at pH 10) and not with its salt or with the unalkylated carboline, has been discussed on the basis of the canonical formula of the anhydronium base in the β-carboline system in which the *p*-quinoid structure might be responsible for the ease of hydrogenation (Scheme 12.17).[126]

12.1.6.2 Phenanthrolines. Searles and Warren hydrogenated 4,7-phenanthroline (**39**) over Raney Ni in ethanol in the presence of sodium ethoxide and obtained a mixture of 5,6-dihydro and 1,2,3,4-tetrahydro derivatives (eq. 12.67).[127] In the case of 2-methylphenanthroline, 2-methyl-7,8,9,10-tetrahydrophenanthroline was produced concurrently with 2-methyl-5,6-dihydrophenanthroline.



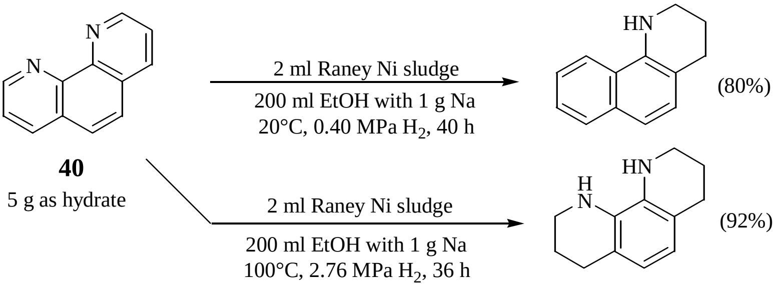
Scheme 12.17 Canonical formula of the anhydronium base in the β-carboline system.



(12.67)

When 4,7-phenanthroline was hydrogenated over platinum oxide in 1:1 AcOH-EtOH at near-atmospheric pressure, about 2 mol of hydrogen were taken up and the product was a mixture from which only 1,2,3,4-tetrahydrophenanthroline was isolated in nearly 40% yield.[128]

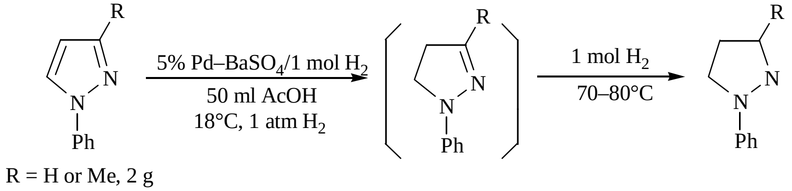
Hydrogenation of 1,10-phenanthroline (**40**) with Raney Ni under conditions similar to those used for **39** afforded the 1,2,3,4-tetrahydro derivative in 80% yield (eq. 12.68), and there was no evidence of the formation of the 5,6-dihydro derivative.[129] When the hydrogenation was performed at 100°C and 2.76 MPa H_2 for 36 h, an almost quantitative yield of 1,2,3,4,7,8,9,10-octahydrophenanthroline was obtained (eq. 12.68), indicating that the two pyridine rings are much more susceptible to hydrogenation than the benzene ring over Raney Ni.



(12.68)

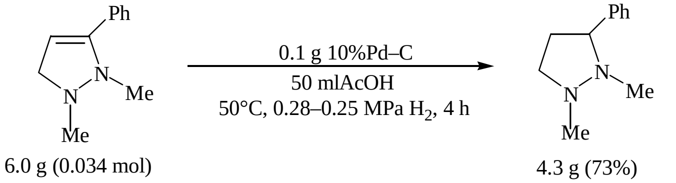
12.1.7 Compounds with More than One Nitrogen Atom in the Same Ring

12.1.7.1 Pyrazoles, Imidazoles, and Related Compounds. Thoms and Schnupp hydrogenated pyrazole to 2-pyrazoline in ethanol-acetic acid over 5% Pd–$BaSO_4$ at 18°C. The hydrogenation of 1-phenyl- and 3-methyl-1-phenylpyrazoles at room temperature became very slow after the absorption of 1 mol of hydrogen and further uptake of hydrogen to give pyrazolidines occurred at 70–80°C with or without the addition of a new portion of the catalyst (eq. 12.69).[130]



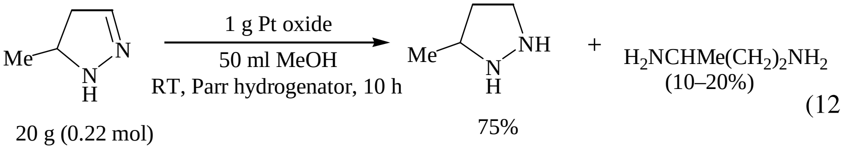
(12.69)

1,2-Dimethyl-3-phenyl-3-pyrazoline was hydrogenated to the corresponding pyrazolidine in a 73% yield over Pd–C in acetic acid at 50°C and 0.28–0.25 MPa H_2 (eq. 12.70).[131]



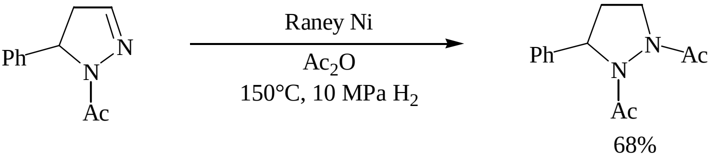
(12.70)

Hydrogenation of 2-pyrazolines over platinum oxide in methanol led to the pyrazolidines containing 10–20% of the 1,3-diamines resulting from the hydrogenolysis of the N–N bond.[132] With 5-methyl-2-pyrazoline the corresponding pyrazolidine was obtained in a 75% yield, although some 10–20% of hydrogenolysis of the N–N bond accompanied the hydrogenation (eq. 12.71).

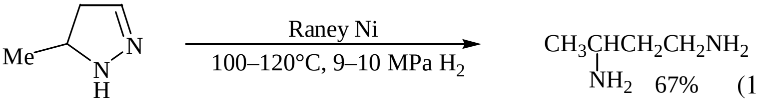


(12.71)

Generally, the N–N bond may be stabilized toward hydrogenolysis by acetylation or hydrogenation in acetic anhydride, as in eq. 12.72 in the Raney Ni–catalyzed hydrogenation of a pyrazoline derivative at a high temperature and pressure.[133] In contrast, 5-methylpyrazoline was hydrogenolyzed to give butane-1,3-diamine in 67% yield under even milder conditions (eq. 12.73).[134]

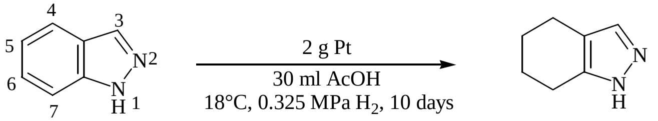


(12.72)



(12.73)

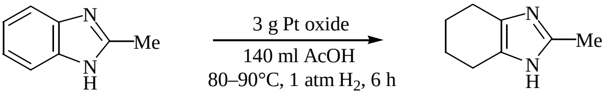
1*H*-Indazole (benzopyrazole) (**41**) was not reduced over Pd–$BaSO_4$ in acetic acid at room temperature and 0.325 MPa H_2 and could be hydrogenated only very slowly with use of an unusually high catalyst ratio of platinum (eq. 12.74).[135] 2-Methylindazole was hydrogenated much more rapidly than 1-methylindazole and indazole; the latter was hydrogenated more slowly. The products were always the corresponding 4,5,6,7-tetrahydro compounds, although hydrogenation usually occurs at the pyrazole ring with phenyl-substituted pyrazoles.[135]



41
1.18 g (0.01 mol)

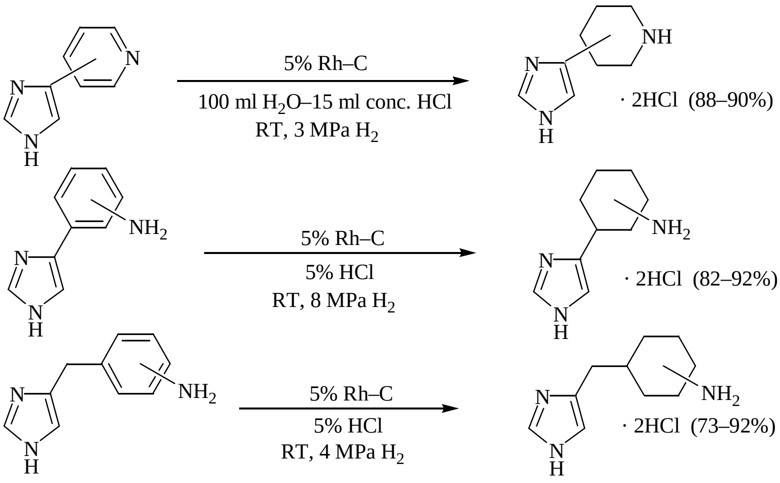
(12.74)

Imidazoles are rarely not hydrogenated under mild conditions.[136] Pyridyl-, aminophenyl-, and aminobenzyl-substituted imidazoles may be hydrogenated to the corresponding piperidyl and cyclohexanoid derivatives in high yields without affecting the imidazole ring over Rh–C in dilute hydrochloric acid, as shown in Scheme 12.18.[137–139] Benzimidazole was reported not to be hydrogenated over nickel catalyst.[140,141] The results were also confirmed by Hartmann and Panizzon, who could not hydrogenate benzimidazole with nickel catalyst even at 200°C at a high hydrogen pressure or with platinum catalyst at 100°C in various solvents.[142] On the other hand, 2-methyl- (eq. 12.75), 2-ethyl-, 1,2-dimethy-, and 2-phenylbenzimidazoles were hydrogenated in the benzene ring in good yields over platinum oxide in acetic acid without affecting the imidazole ring. However, benzimidazoles substituted only in the 1 position or with substituents in the benzene ring, such as 1-methyl-, 2,5-dimethyl-, and 1-ethyl-2,6-dimethylbenzimidazoles, were not hydrogenated.[142]



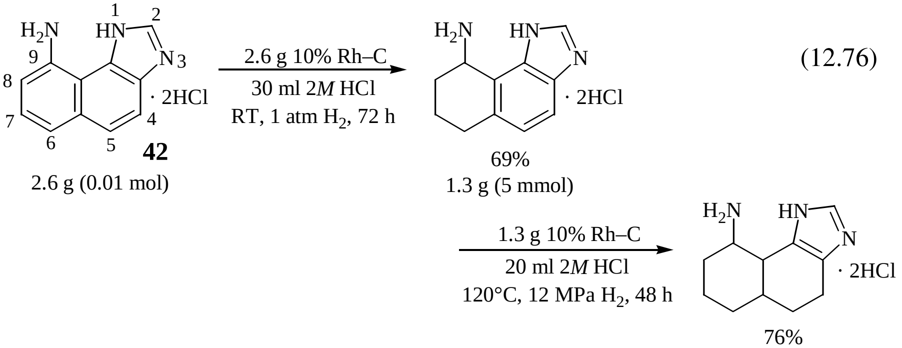
(12.75)

19 g (0.14 mol) 17 g (87%)



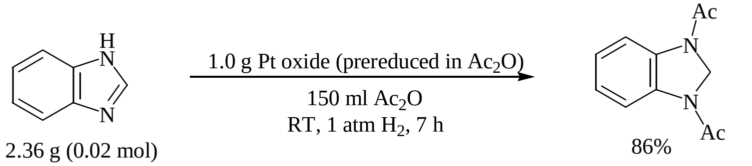
Scheme 12.18 Hydrogenation of imidazole derivatives over Rh–C catalyst.

4-Aminomethylbenzimidazole dihydrochloride was hydrogenated to the 4,5,6,7-tetrahydro derivative over 10% Rh–C in 3*M* hydrochloric acid in 72 h at ordinary conditions.[143] 9-Aminonaphth[2,1-*d*]imidazole dihydrochloride (**42**) was hydrogenated to the 6,7,8,9-tetrahydro derivative under similar conditions and further to the octahydronathimidazole at 120°C and 12 MPa H_2 in 48 h (eq. 12.76).



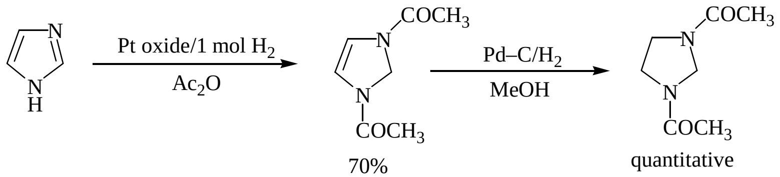
(12.76)

In acetic anhydride as the solvent, however, imidazole was smoothly hydrogenated over platinum oxide at room temperature and atmospheric pressure to give 1,3-diacetylimidazolidine in 80% yield.[144] Under the same conditions, benzimidazole was hydrogenated to give 1,3-diacetylbezimidazoline in 86% yield, leaving the benzene ring unchanged (eq. 12.77). Thus the stable structure of the amidine moiety toward hydrogenation appears to be largely modified by the acetylation.

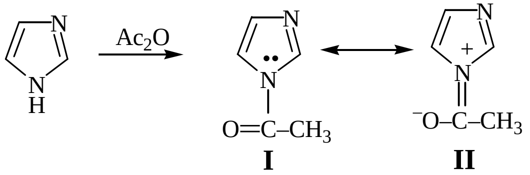


(12.77)

Butula hydrogenated imidazole and benzimidazole over Pd–$BaSO_4$ in acetic acid added in portions with 4 equiv of acetic anhydride, and obtained 1,3-diacetylimidazolidine and 1,3-diacetylbenzimdazoline in 70 and 72% yields, respectively.[145] Hydrogenation of imidazole in acetic anhydride over platinum oxide absorbed 1 mol of hydrogen faster and gave 1,3-diacetyl-4-imidazoline in 70% yield. The imidazoline was hydrogenated to the corresponding imidazolidine quantitatively over Pd–C in methanol (Scheme 12.19). Since 1-acetylimidazole was easily hydrogenated over Pd–



Scheme 12.19 Formation of 1,3-diacetyl-4-imidazoline from imidazole and its hydrogenation to imidazolidine derivative.

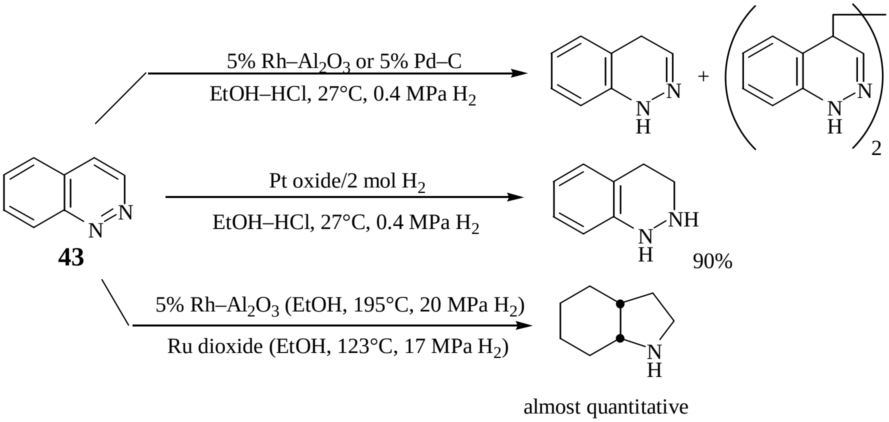


Scheme 12.20 Formation of 1-acetylimidazole from imidazole and its canonical structures.

$BaSO_4$ in acetic acid, the first stage of the hydrogenation of imidazole in acetic anhydride was suggested to be the formation of 1-acetyimidazole, in which the lone electron pair on the nitrogen atom in structure **I** may participate in the mesomeric form **II** (Scheme 12.20). The double bonds in the imidazole ring thus localized may become subject to hydrogenation more easily.[145]

12.1.7.2 Pyridazine, Pyrimidine, Pyrazine, and Related Compounds.

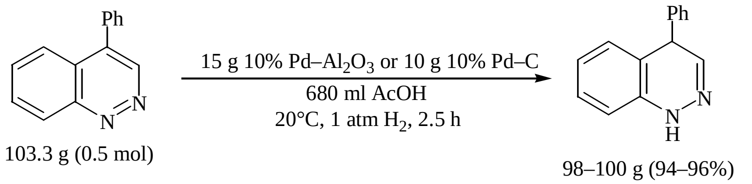
Pyridazine is stable toward hydrogenation at the conditions under which 3-chloro- and 3,6-dichloropyridazines are hydrogenolyzed to form pyridazine over Pd–C catalyst (room temperature and 0.3 MPa H_2).[146,147] Cinnoline (benzo[*c*]pyridazine) (**43**) was hydrogenated to the 1,4-dihydro derivative, along with the corresponding dimerized product, over Rh–Al_2O_3 or Pd–C in ethanol containing hydrogen chloride. Hydrogenation over platinum oxide in ethanol containing hydrogen chloride with uptake of 2 mol of hydrogen afforded the 1,2,3,4-tetrahydro derivative in 90% yield, along with small amounts of 2-aminophenethylamine, indole, and dihydroindole. With uptake of 4 mol of hydrogen, the yield of the tetrahydro compound decreased to 64% and the yield of the phenethylamine increased to 22%. The hydrogenation in ethanol over 5% Rh–Al_2O_3 at 195°C and 20 MPa H_2 or over ruthenium dioxide at 123°C and 17 MPa H_2 led to almost quantitative formation of *cis*-octahydroindole.



Scheme 12.21 Hydrogenation products of cinnoline under various conditions.

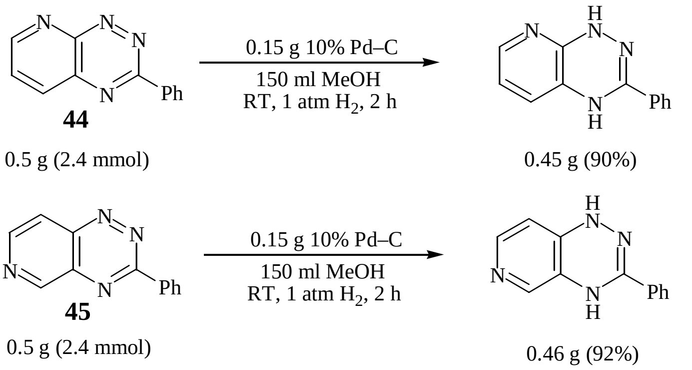
The hydrogenation products of cinnoline under various conditions are summarized in Scheme 12.21.[148]

The 1,4-dihydro product was formed almost quantitatively in the hydrogenation of 4-phenylcinnoline over 5% Pd–Al_2O_3 in acetic acid (eq. 12.78).[149] Hydrogenation over platinum in acetic acid might lead to formation of the tetrahydro derivative, since 4-phenyldihydrocinnoline was hydrogenated to the tetrahydro compound under this condition.[150] In ethanol, however, 3,4-diphenyl- and 7-methyl-3,4-diphenylcinnolines were hydrogenated to yield the corresponding 1,4-dihydro derivatives over platinum oxide.[151]



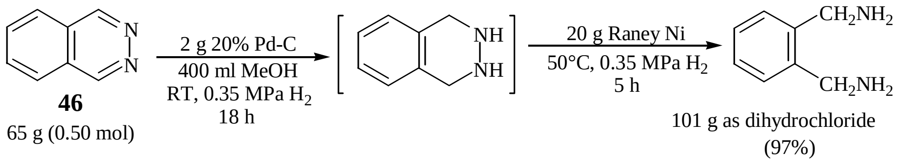
(12.78)

The 1,4-dihydro derivatives have also been obtained in high yields in the hydrogenation of pyrido-*as*-triazines **44** and **45** over Pd–C in methanol (eq. 12.79).[152]



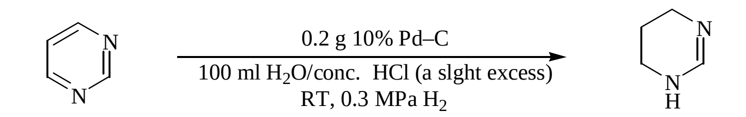
(12.79)

Phthalazine (**46**) was hydrogenated by Elslager et al. to prepare 1,2-bis(aminomethyl)benzene (*o*-xylene-α,α′-diamine).[153] An overall yield of 97% was obtained by the hydrogenation in two stages using Pd–C and Raney Ni as the catalysts for the respective stages. For the first stage, in which 2 mol of hydrogen was absorbed and hydrogenation to 1,2,3,4-tetrahydrophthalazine presumably involved, 20% Pd–C was employed as the catalyst. For the second stage, which involved the absorption of 1 mol of hydrogen corresponding to the hydrogenolysis of the N–N bond, Raney Ni was used as the catalyst (eq. 12.80).[153]



(12.80)

According to Smith and Christensen, the pyrimidine ring is usually stable toward catalytic hydrogenation in neutral or basic medium under mild conditions.[154] Haggerty, Jr. et al., however, found that, while 4-methylpyrimidine was only partially hydrogenated under neutral conditions to the corresponding dihydropyrimidine in the presence of Pd–C in 20 h, 2-methylpyrimidine absorbed 1 mol of hydrogen essentially completely in 30 min.[155] The uptake of hydrogen by 2-methylpyrimidine was also observed in basic media with either Pd–C or Raney Ni. On the other hand, pyrimidine and its derivatives may be readily hydrogenated in the presence of acid to 1,4,5,6-tetrahydro derivatives,[154,156] which possess an amidine moiety resistant to hydrogenation under mild conditions. Thus pyrimidine and 2-, 4-, and 5-methylpyrimidines were hydrogenated in 97–98% yields to the corresponding 1,4,5,6-tetrahydro derivatives over 10% Pd–C in the presence of a slight excess of concentrated hydrochloric acid at room temperature and an initial hydrogen pressure of 0.3 MPa (eq. 12.81).[154]

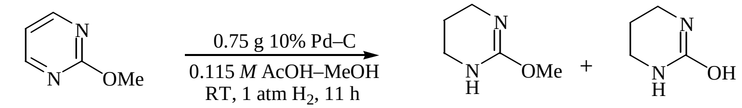


(12.81)

2 g (0.025 mol)

98% (as HCl salt)

Hydrogenation of 2-aminopyrimidine under acidic conditions, however, gave the dihydro derivative exclusively, although 2-amino-4,6-dichloropyrimidine yielded 2-amino-1,4,5,6-tetrahydropyrimidine in neutral hydrogenation. The 4-amino- and 5-aminopyrimidines behaved similarly to the 2-aminopyrimidine. Hydrogenation in acid solution of 2,4,6-trimethyl-, 2-hydroxy-, 2-methoxy-, and 5-methoxypyrimidines also gave the corresponding 1,4,5,6-tetrahydro derivatives.[156] Because of the lability of the methoxyl group in aqueous acid, it was necessary to employ methanolic acetic acid as a hydrogenation medium for 2-methoxypyrimidine (eq. 12.82).



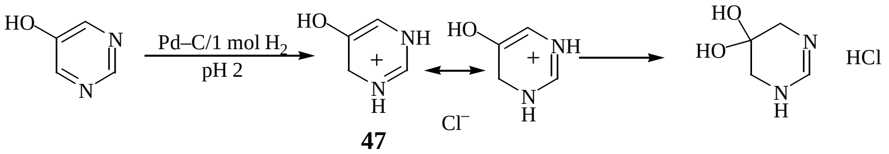
1.5 g (0.019 mol)

0.3 g (isolated as HCl salt)

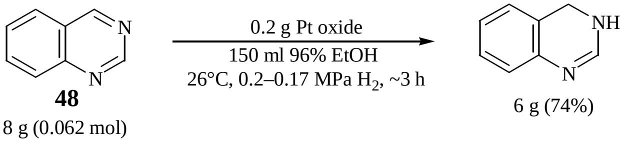
0.42 g

(12.82)

5-Hydroxypyrimidine, which is unstable to strong acids, could be hydrogenated at pH 2 with the absorption of only 1 mol of hydrogen. The initial product **47** tautomerized and hydrated to give 1,4,5,6-tetrahydro-5,5-dihydroxypyrimidine (Scheme 12.22). 5-Methoxypyrimidine, however, underwent smooth hydrogenation in dilute acid to yield the corresponding 1,4,5,6-tetrahydro compound. Hydrogenation of 5-acetamidopyrimidine in hot (100°C) acetic anhydride, used as a solvent to avoid hydrolysis, gave 5-acetamido-1,3-diacetyl-1,2,3,4-tetrahydropyrimidine, which was further hydrogenated to a hexahydro derivative over platinum oxide in 1-propanol (Scheme 12.23).[156] Quinazoline (**48**) is rather easily hydrogenated to the 3,4-dihydro derivative over platinum oxide in ethanol at room temperature (eq. 12.83).[157] The hydrogenation may be facilitated with use of an aqueous acidic medium, which might be especially favorable for the quinazolines with an electron-releasing substituent in the 4-position.

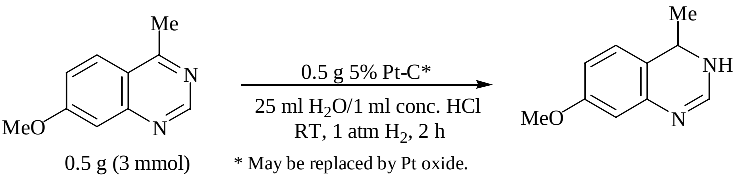


Scheme 12.22 Hydrogenation of 5-hydroxypyrimidine at pH 2.



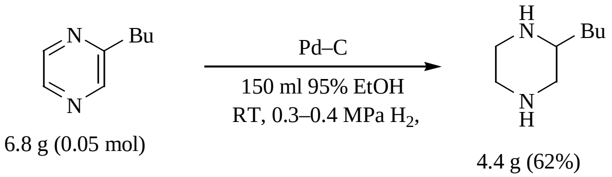
(12.83)

The electron-releasing 4-substituents are considered to stabilize the 3,4 double bond toward hydrogenation. An electron-releasing 7-substituent (OMe, NH_2, or OH) may also contribute to the stabilization of the 3,4 double bond. Thus the hydrogenation of 7-methoxy-4-methylquinazoline to the 3,4-dihydro derivative was successful only in aqueous hydrochloride or aqueous acetic acid, using palladium and platinum catalysts (eq. 12.84).[158] No reduction took place at room temperature in nonaqueous solvents such as ethanol, ethanol–HCl, and acetic acid.

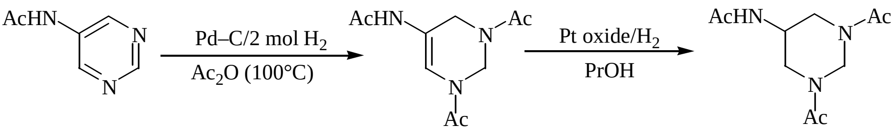


(12.84)

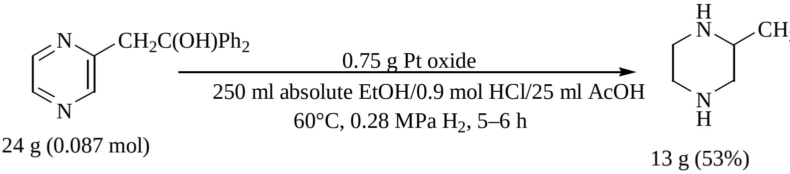
2-Substituted pyrazines were hydrogenated to the corresponding piperazines over Pd–C in 95% ethanol (eq. 12.85),[159] or over platinum oxide in methanol[160] or in absolute ethanol containing dry hydrogen chloride and acetic acid (eq. 12.86).[161]



(12.85)



Scheme 12.23 Hydrogenation of 5-acetamidopyrimidine.

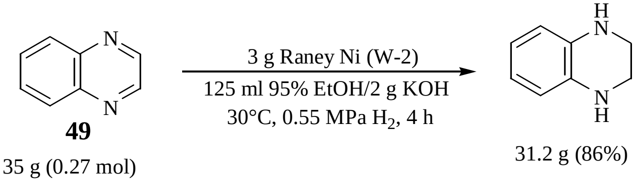


(12.86)

Hydrogenation of 2,3,5,6-tetramethylpyrazine over platinum oxide was unsuccessful in alcohol or in ethyl acetate, and proceeded only to small extents in acetic acid. However, the anhydrous hydrochloride of the pyrazine was rapidly and quantitatively hydrogenated in absolute ethanol with the addition of acetic acid.[162] The methiodide of the tetramethylpirazine was also successfully hydrogenated over platinum oxide in ethanol with the addition of a little water.[163]

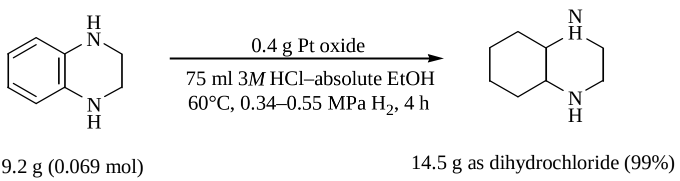
With nickel catalysts, the hydrogenation of pyrazines requires more vigorous conditions.[164–166] 2,5-Dimethylpyrazine was hydrogenated to *trans*-2,5-dimethylpiperazine at 220–225°C and 3–4 MPa H_2 over Ni–Al_2O_3 in 80% yield.[166] 2-Methylpiperazine of high purity (92% yield, 99.99% purity) was obtained by hydrogenation of 2-methylpyrazine over Raney Ni in *i*-PrOH in the presence of ammonia at 140°C and 4.9 MPa H_2.[167]

The hydrogenation of quinoxaline (**49**) in acetic acid over platinum oxide, in hydrochloric acid over Pd–C, and in hydrochloric acid over platinum oxide led to hydrogen uptake corresponding to no definite compound, much tar was formed, and no single pure substance was isolated.[168] Hydrogenation of quinoxaline in absolute ethanolic hydrogen chloride absorbed only one atom of hydrogen per molecule of quinoxaline, giving an intensely blue solid whose color faded on exposure to air. A pure tetrahydro derivative was obtained in 85–90% yields when quinoxaline was hydrogenated in a basic solution of ethanol over Raney Ni (eq. 12.87).



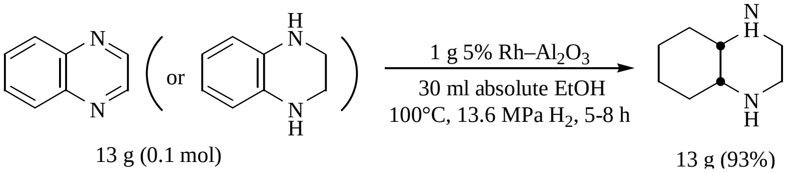
(12.87)

Tetrahydroquinoxaline was hydrogenated to the decahydro derivative over platinum oxide in acetic acid,—better—in an absolute ethanolic hydrogen chloride (eq. 12.87). In ethanolic aqueous hydrogen chloride or aqueous hydrochloric acid, considerable hydrogenolysis occurred to give a mixture of decahydroquinoxaline and *N*-cyclohexylethylenediamine, and also neutral substances (e.g., cyclohexanol) in the latter solvent.[168]



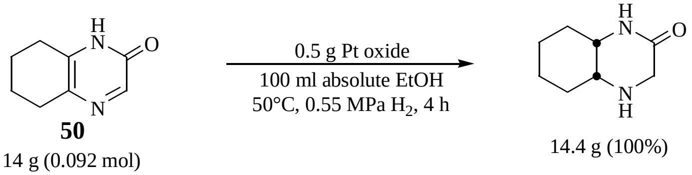
(12.88)

Broadbent et al. have shown that the decahydroquinoxaline obtained by Christie et al. (eq. 12.88) is a mixture of the *trans* isomer (mp 150–151°C) and the *cis* isomer (mp 56–58°C), and could obtain pure *cis*-decahydroquinoxaline in high yields by hydrogenation of quinoxaline or tetrahydroquinoxaline over either freshly prepared Raney Ni (W-6) or, preferably, 5% Rh–Al_2O_3 at 100°C and 13.6 MPa H_2 (eq. 12.89).[169]



(12.89)

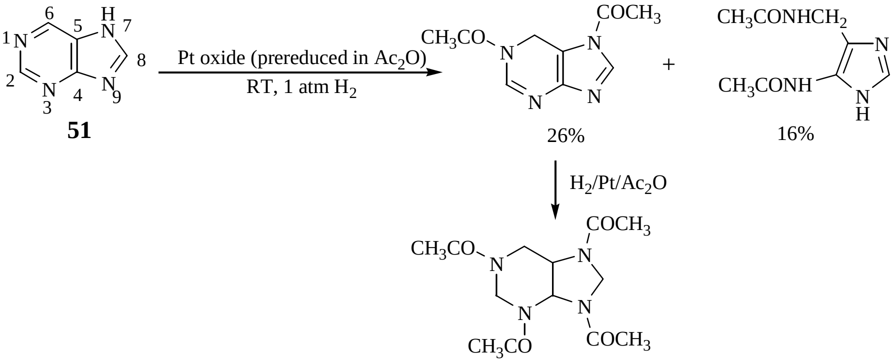
Subsequently, Brill and Schultz hydrogenated 5,6,7,8-tetrahydro-2-quinoxalone (**50**), prepared by condensing 1,2-cyclohxanedione with glycinamide, over platinum oxide to give quantitative yield of *cis*-decahydro-2-quinoxalone (eq. 12.90), which was transformed into *cis*-decahydroquinoxaline by reduction with lithium aluminum hydride.[170]



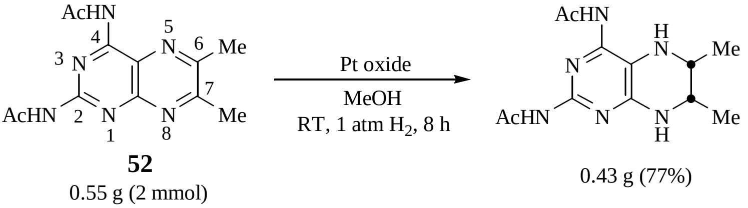
(12.90)

Purine (**51**) is not hydrogenated in water over Pd–C at room temperature and atmospheric pressure or affected during the dechlorination of 6-chloropurine and 2,6-dichloro-7-methylpurine under the same conditions.[171] However, absorption of hydrogen occurred to an extent of 94% of theory (for 1 mol) with the addition of an equivalent quantity of hydrochloric acid. According to Butula, hydrogenation of purines over platinum and palladium occurs initially in the 1,6 positions.[172] Butula hydrogenated purine hydrochloride or 6-chloropurine over Pd–$BaSO_4$ in acetic acid and obtained 1,6-dihydropurine in 40–60% yields. Hydrogenation of purine in acetic anhydride over platinum or palladium catalyst gives 1,7-diacety-1,6-dihydropurine along with a small amount of 4-acetaminomethyl-5-acetaminoimidazole. The 1,6-dihydropurine obtained is hydrogenated further to 1,3,7,9-tetraacetylperhydropurine in acetic anhydride (Scheme 12.24).[172]

Hydrogenation of pteridines usually occurs in the pyrazine ring to yield the 5,6,7,8-tetrahydro products, since the pyrimidine ring is much more stable toward hydrogenation. 2,4-Diacetamino-6,7-dimethylpteridine (**52**) was hydrogenated to the corresponding *cis*-5,6,7,8-tetrahydro derivative in methanol over platinum oxide at the ordinary conditions (eq. 12.91).[173] The 5,6,7,8-tetrahydro product was also obtained in the Raney Ni–catalyzed hydrogenation of 4-amino-7-methyl-2-phenylpteridine in ethanol at room temperature and 0.34 MPa H_2.[174]

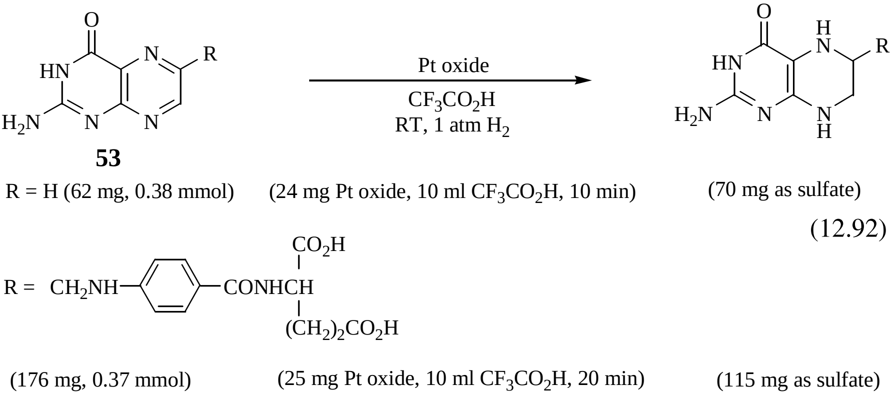


Scheme 12.24 Hydrogenation of purine over platinum catalyst in acetic anhydride.



(12.91)

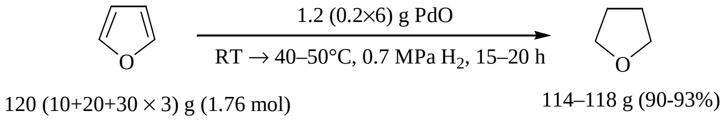
Hydrogenation of pterin (2-amino-4-oxo-3,4-dihydropteridine) (**53**, R = H) was very slow in 1*M* NaOH. The best results were obtained in hydrogenation over platinum or rhodium in trifluoroacetic acid. The hydrogenation in trifluoroacetic acid was about 30 times faster than that in 1*M* HCl, which gave the best results among aqueous hydrochloric acids of various concentrations. Thus pterin and folic acid were selectively hydrogenated in the pyrazine ring in trifluoroacetic acid over platinum oxide in quite short times (eq. 12.92).[175]



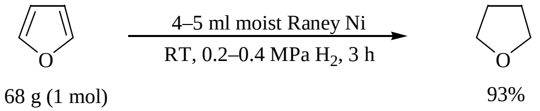
12.2 *O*-HETEROCYCLES

12.2.1 Furans and Related Compounds

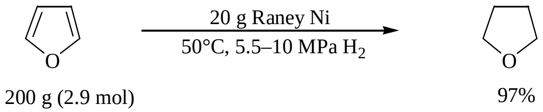
The hydrogenation of furan rings generally occurs under conditions considerably milder than those used for the benzene nucleus, if well-purified materials are subjected to hydrogenation. However, furans, which are unsaturated cyclic ethers, may undergo the cleavage of the ether linkages in the course of the ring hydrogenation. Under vigorous conditions the tetrahydrofurans formed may also be susceptible to the ring-opening reaction. Usually, high yields of tetrahydrofurans are obtained by hydrogenation over Ni–kieselguhr, Raney Ni, palladium, rhodium, and ruthenium catalysts. The hydrogenation of furan was performed without solvent over palladium oxide[176] and Raney Ni[176–179] or by using a solvent with Raney Ni.[180] Hydrogenation may occur at low pressures and at temperatures ranging from room temperature up to 40–60°C over both the palladium and nickel catalysts (eqs. 12.93[176] and 12.94[178]), although application of higher temperatures and pressures might be advantageous, especially with the latter catalyst[176,177,181] (eq. 12.95[179])



(12.93)

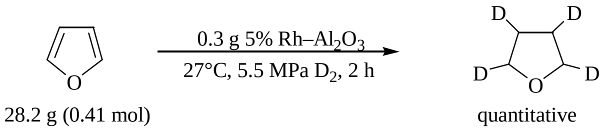


(12.94)



(12.95)

Tetrahydrofuran-2,3,4,5-d_4 was prepared by deuteration over 5% Rh–Al_2O_3 at 27°C and an initial deuterium pressure of 5.5 MPa (eq. 12.96).[182]



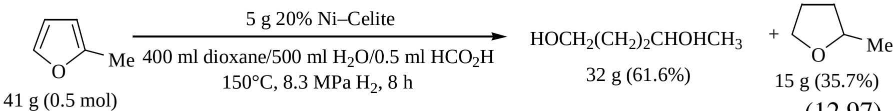
(12.96)

2-Alkylfurans were hydrogenated to 2-alkyltetrahydrofurans in high yields over Ni–kieselguhr or Raney Ni at elevated temperatures and pressures.[183–185] However, it was noted that the hydrogenation of 2-methylfuran without a solvent over Raney Ni at 100°C and 16 MPa H_2, which gave an 80% yield of 2-methyltetrahydrofuran with 10 wt% of catalyst, resulted in a lower yield of 65% in a larger run with 6.5 wt% of catalyst due to some ring cleavage, since an exothermic reaction carried the temperature to 140°C.[185]

Vapor-phase hydrogenation of 2-methylfuran over a nickel catalyst gave 2-methyltetrahydrofuran as the chief product (86% yield) at 100°C, but as the temperature was raised, the amount of the tetrahydro compound decreased with formation of increased amounts of 2-pentanone, which attained a maximum (75% yield) at about 185°C. Along with the ketone, a small amount of 2-pentanol was also formed.[186]

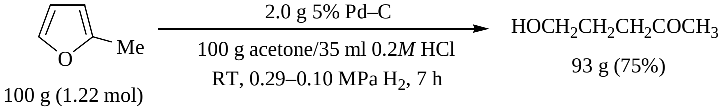
2-Arylfurans are extensively hydrogenolyzed to give the ring-opened products over Raney Ni as well as over palladium catalysts. Thus 4-phenyl-1-butanol was obtained quantitatively in the hydrogenation of 2-phenylfuran over Raney Ni in ethanol at 45–50°C or over 5% Pd–C in acetic acid at 30–35°C under an atmospheric pressure of hydrogen.[187] It has also been observed that over Raney Ni, 2-phenyltetrahydrofuran is less readily hydrogenolyzed than 2-phenylfuran but as readily over Pd–C.[188]

Hydrogenation of 2-methylfuran in the presence of water leads to the formation of 5-hydroxy-2-pentanone and 1,4-pentanediol.[189,190] Schniepp et al. obtained 5-hydroxy-2-pentanone in 25–35% yields or 1,4-pentanediol in 50–60% yields, together with 2-methylterahydrofuran, by hydrogenation of 2-methylfuran in the presence of water and formic acid in concentrations of 0.01–0.10 wt% of the reaction mixture using a reduced Ni–on-Celite as catalyst (eq. 12.97).[190]



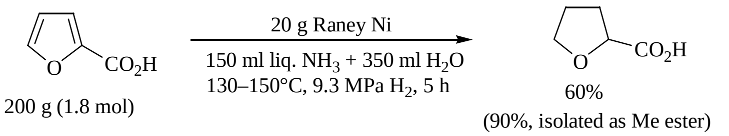
(12.97)

Londergan et al. could obtain 5-hydroxy-2-pentanone in a 75% yield by hydrogenating 2-methylfuran in a mixture of acetone and 0.2*M* hydrochloric acid using 5% Pd–C as catalyst (eq. 12.98).[191]

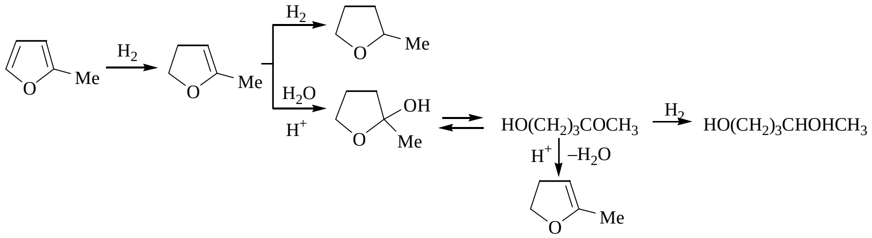


(12.98)

It has been demonstrated that the 4,5-dihydro-2-methylfuran, formed as an intermediate, hydrolyzes to 5-hydroxy-2-pentanone through the reaction sequence shown in Scheme 12.25.[189,190,192] On the other hand, 5-hydroxy-2-pentanone was cyclodehydrated to give 4,5-dihydro-2-methylfuran in yields of 86% or more in a continuous process in the presence of phosphoric acid (Scheme 12.25). Furan-2-carboxylic acid (2-furoic acid) was hydrogenated to the corresponding tetrahydro derivative in water over Skita's colloidal palladium at room temperature[193] or over Raney Ni in ammoniacal water at 130–150°C and 0.93 MPa H_2 (eq. 12.99)[194] or as its sodium salt in water at 110°C and 5.2 MPa H_2.[195]

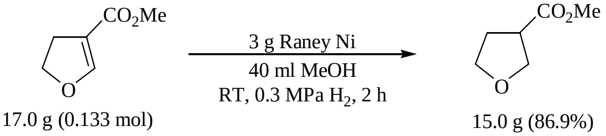


(12.99)

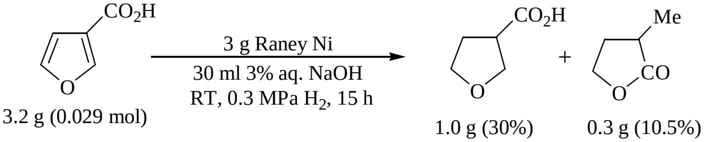


Scheme 12.25 Formation of hydrogenation and hydrolysis products from 2-methylfuran.

Methyl 2-furoate was hydrogenated over Raney Ni in methanol solution at 120°C to give a 90% yield of methyl tetrahydro-2-furoate.[194] 3-Methoxycarbonyl-4,5-dihydrofuran was hydrogenated in high yield to the tetrahydrofuran derivative over Raney Ni in methanol at room temperature and 0.3 MPa H_2 (eq. 12.100), while, in the hydrogenation of furan-3-carboxylic acid over Raney Ni in an aqueous sodium hydroxide, 10.5% of the lactone resulting from ring cleavage was obtained along with 30% of tetrahydrofuran-3-carboxylic acid (eq. 12.101).[196]

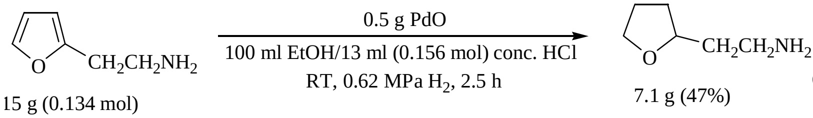


(12.100)



(12.101)

According to Freifelder, in most instances ruthenium catalyst is superior to nickel catalyst for the hydrogenation of furans to tetrahydrofurans; the hydrogenation can be carried out at 70–100°C and 7 MPa H_2.[185] He refers to an example in which 2-furfurylamine was hydrogenated without solvent over ruthenium dioxide at 100°C and 8 MPa H_2 in 10 min, compared to the temperatures of ≤ 150°C and a reaction time of 30 h at 7 MPa H_2 that were required for hydrogenation with Raney Ni. Hydrogenation of β-(2-furyl)alkylamines and an *N*-ethyl-2-furylalkylamine to the corresponding tetrahydro compounds was performed satisfactorily over palladium catalyst in ethanol in the presence of hydrochloric acid at room temperature and 0.62 MPa H_2 (eq. 12.102)[197] and over 5% Rh–C in neutral solvent at room temperature and 0.15 MPa H_2, respectively.[185]

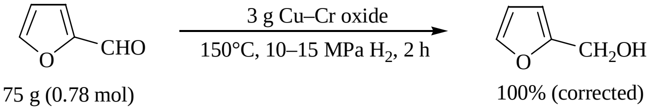


(12.102)

In general, hydrogenation of furans over copper–chromium oxide[183] or over platinum catalysts[198,199] is accompanied by hydrogenolysis of the ether linkage to yield the ring-opened products. For example, hydrogenation of 2-methylfuran over copper–chromium–barium oxide at 250°C and 17.5 MPa H_2 gave only a 15% yield of 2-methyltetrahydrofuran accompanied by 4% of pentane, 33% of 2-pentanol, and 30% of 1-pentanol.[183] Hydrogenation of 2-methylfuran over Adams platinum oxide in acetic acid resulted in the formation of 80–90% of 2-pentanol. Similarly, furfuryl alcohol was hydrogenated to 1,2-pentanediol almost quantitatively over platinum oxide in acetic acid.[199] Extensive hydrogenolysis of furans over platinum and much less hydrogenolysis over palladium appear to reflect the different characteristics of these metals toward hydrogenolysis of an enol-type ether, rather than that for an allyl-type ether.[200]

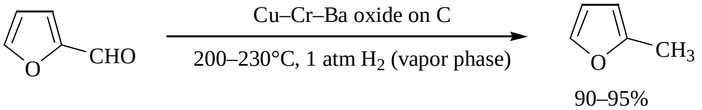
Hydrogenolysis of the carbon–oxygen bonds in furans may occur under much milder conditions than those required for hydrogenolysis of corresponding tetrahydrofurans. For example, over copper–chromium oxide at 250°C and 17.5 MPa H_2, 74% of 2-methyltetrahydrofuran was recovered unchanged after 6 h. Under similar conditions, the hydrogenation of furfuryl alcohol over copper–chromium oxide yielded a mixture of 1,2- and 1,5-pentanediols, while tetrahydrofurfuryl alcohol underwent hydrogenolysis only to a small extent even after 11 h and yielded 1,5-petanediol selectively.[183,201]

Hydrogenation of furfural and related compounds has been the subject of a large number of investigations, since furfural may be prepared industrially by the action of water or dilute acid on pentosan-containing materials such as corncobs, wood, the hulls of oats, rice, and peanuts, and is the most important starting compound for various furans and their derivatives.[202,203] Wojcik reviewed the hydrogenation of furan compounds mostly over Ni–kieselguhr, Raney Ni, and copper–chromium oxide as catalysts.[181] Furfural, although it is an aldehyde of aromatic character, such as benzaldehyde, can be converted to furfuryl alcohol in virtually quantitative yield over copper–chromium oxide as catalyst at high pressures and at temperatures lower than 175°C, at which point the catalyst has little or no effect on the furan ring (eq. 12.103).[71,181] This transformation may also be performed in the presence of other catalysts, although in most cases the hydrogenation tends to proceed over the stage of furfuryl alcohol.



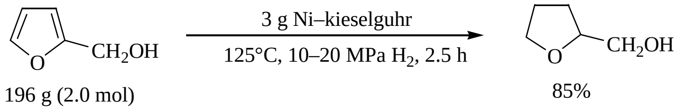
(12.103)

Conversion of furfural to 2-methylfuran was achieved in 90–95% yields by vapor-phase hydrogenation over copper–chromium–barium oxide dispersed on activated charcoal at 1 atm H_2 and 200–230°C (eq. 12.104).[204]

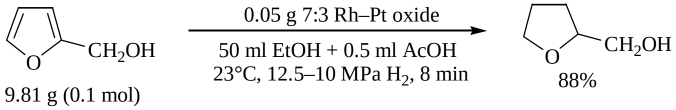


(12.104)

Furfural was converted to tetrahydrofurfuryl alcohol in 96–98% yields by hydrogenation over copper–chromium oxide at 150–160°C and 10–20 MPa H_2, followed by hydrogenation with added Raney Ni at 100–115°C.[205a] The hydrogenation was performed in one step in 70–80% yields with use of either Raney Ni or a mixture of copper–chromium oxide and Raney Ni at 170–180°C and 6.9–10.3 MPa H_2.[181] Tetrahydrofurfryl alcohol was also obtained in 73% yield in hydrogenation over a ruthenium catalyst in ethanol in the presence of magnesium oxide at 110°C and 15 MPa H_2,[205b] although a better yield (89%) was reported in the hydrogenation over ruthenium dioxide at 100°C and 10 MPa H_2.[206] Tetrahydrofurfuryl alcohol is usually obtained in higher yields by hydrogenation of furfuryl alcohol than of furfural. The hydrogenation of furfuryl alcohol over Ni–kieselguhr at 125°C and 10–20 MPa H_2 gave tetrahydrofurfuryl alcohol in 85% yield (eq. 12.105).[207] Tetrahydrofurfuryl alcohol was also obtained in an 88% yield in hydrogenation over an Adams-type rhodium–platinum oxide in ethanol with addition of a small amount of acetic acid at 23°C and 12.5–10 MPa H_2 (eq. 12.106).[208]

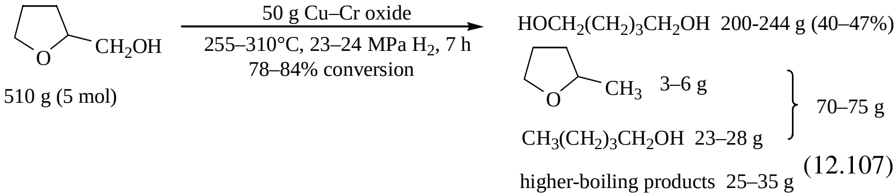


(12.105)



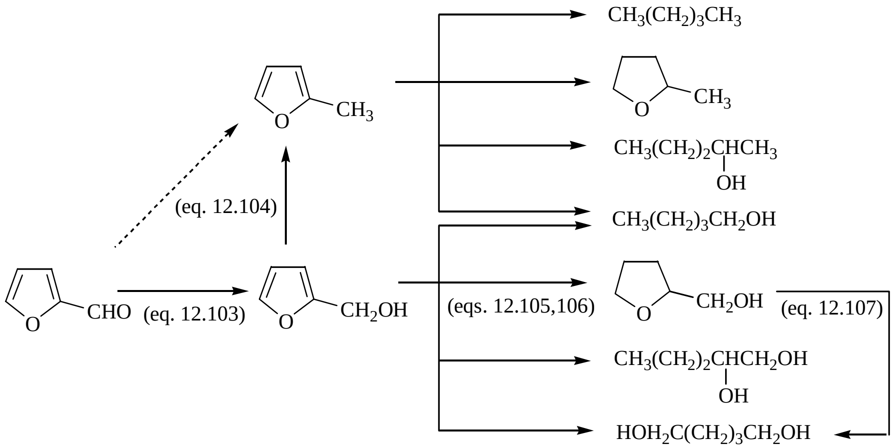
(12.106)

Hydrogenation of furfuryl alcohol over copper–chromium oxide or platinum oxide tends to be accompanied by extensive hydrogenolysis to give the ring-opened products. Hydrogenation of furfuryl alcohol over copper–chromium oxide at 175°C and 10–15 MPa H_2 gave a 70% yield of 1,2- and 1,5-pentanediols, composed of 4 parts of 1,2-diol and 3 parts of 1,5-diol, along with a 10% yield of 1-pentanol and some methyltetrahydrofuran and tetrahydrofurfuryl alcohol.[71] As noted previously, hydrogenation of teteahydrofurfuryl alcohol requires higher temperatures and gives 1,5-pentanediol selectively, rather than the 1,2-diol (eq. 12.107).[183,201]



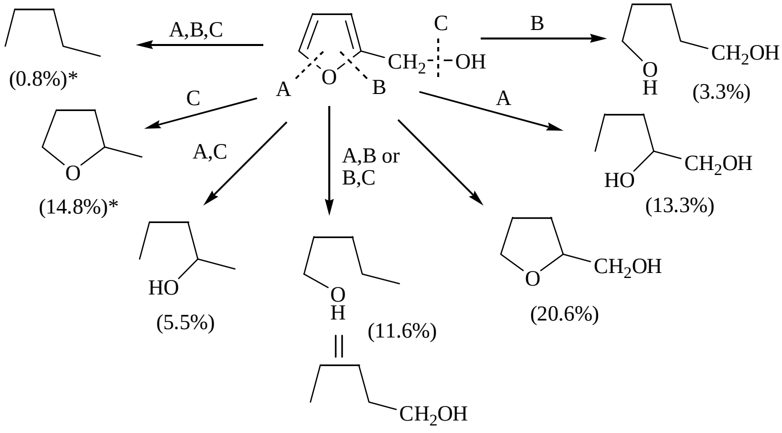
(12.107)

The hydrogenation and hydrogenolysis pathways and products of furfural and furfuryl alcohol are summarized in Scheme 12.26. Hydrogenation of furfural over Adams platinum oxide in ethanol in the presence of ferrous chloride at room temperature and 1–2 atm H_2 first led to quantitative formation of furfuryl alcohol, which was further hydrogenated to a mixture of 1-pentanol (11%), tetrahydrofurfuryl alcohol (35%),



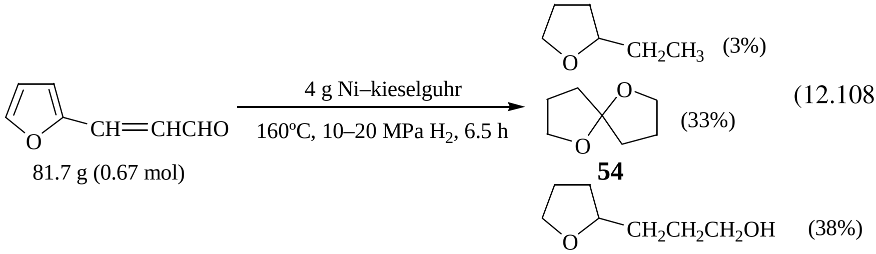
Scheme 12.26 The hydrogenation and hydrogenolysis pathways and products of furfural and furfuryl alcohol.

1,2-pentanediol (20%), and 1,5-pentanediol (8%) with the uptake of 3.2–4.3 mol of hydrogen.[198] Hydrogenolysis of furfuryl alcohol over platinum oxide occurs more extensively in acidic media.[199,209] Hydrogen uptake in the hydrogenation at room temperature and atmospheric pressure increased with respect to the solvent in the order: AcOH (2.86 mol) < EtOH–HCl (3.11 mol) < AcOH–HCl (3.38 mol). In ethanol or tetrahydrofurfuryl alcohol with hydrochloric acid, all seven compounds that were expected to result from the cleavage of the three carbon–oxygen bonds were obtained in the amounts shown in Scheme 12.27.[209]



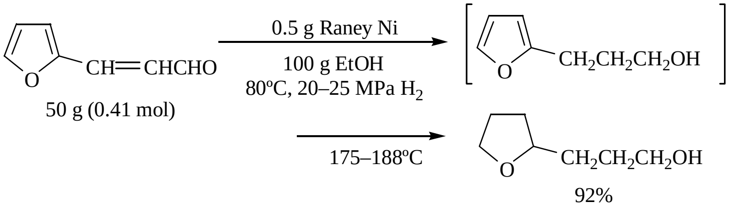
Scheme 12.27 Products of hydrogenation and hydrogenolysis of furfuryl alcohol over Adams platinum oxide in ethanol + 0.5 vol% 3*M* HCl at room temperature and atmospheric pressure (* tetrahydrofurfuryl alcohol instead of ethanol was used as solvent for isolation of these compounds).

Adkins and co-workers found that hydrogenation of 3-(2-furyl)acrolein over nickel catalysts was accompanied by the formation of 1,6-dioxaspiro[4.4]nonane (**54**) (eq. 12.108).[207,210] The amount of the spiro compound **54** formed was greater over Ni–kieselguhr than over Raney Ni. Furfuralacetone[211,212] and difurfuralacetone[212] were also found to yield the same type of products. Burdick and Adkins concluded that 3-(2-furyl)propionaldehyde was an intermediate leading to the formation of **54**, rather than 3-(2-furyl)-1-propanol, since **54** was not formed when the 3-furylpropanol was hydrogenated over Raney Ni.[207] Later studies by Alexander et al. on furfuralacetone and its hydrogenation products showed that Raney Ni promoted rapid and complete hydrogenations to 2-(3-hydroxybutyl)tetrahydrofuran and that copper–chromium oxide and Ni–kieselguhr always gave appreciable amounts of 2-methyl-1,6-dioxaspiro[4.4]nonane.[213] Since 1-(2-furyl)-3-butanol and 3-(2-furyl)-1-propanol were found to give considerable amounts of the spiro–type products over Ni–kieselguhr, it was concluded that the γ-(2-furyl)alkanols are the intermediates leading to these spiranes, which may be formed by the intramolecular addition of the hydroxyl group to a 4,5-dihydrofuryl intermediate (Scheme 12.28).

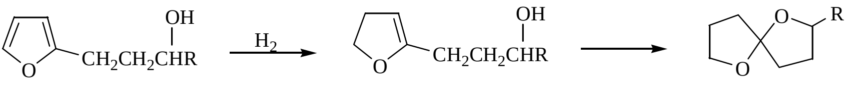


(12.108)

To depress the formation of the spiro-type compound and obtain a high yield of the tetrahydrofurylpropanol from furylacrolein, it proved effective to hydrogenate it with Raney Ni in a dilute ethanol solution, first at 80°C to reduce the side chain and then at 175–188°C to hydrogenate the furan ring (eq. 12.109).[211]

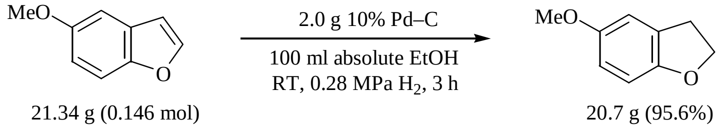


(12.109)



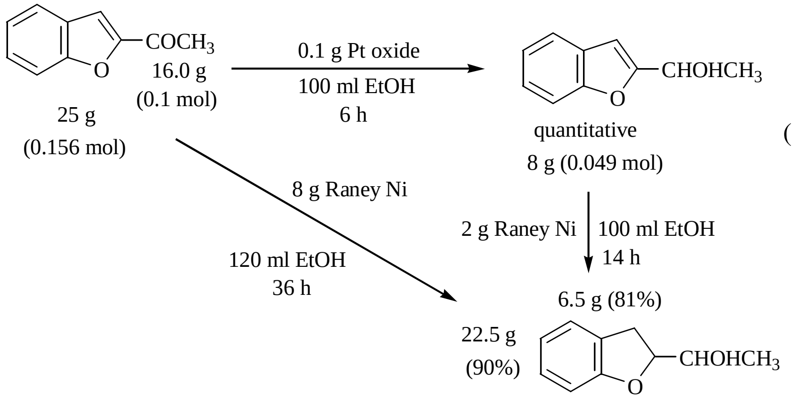
Scheme 12.28 The pathway leading to the formation of 1,6-dioxaspiro[4,4]nonanes in hydrogenation of γ-(2-furyl)alkanols.

Benzo[*b*]furans (coumarones) are readily hydrogenated to the 2,3-dihydro derivatives over palladium and nickel catalysts under mild conditions. Thus 5-methoxybenzofuran was hydrogenated to 2,3-dihydro-5-benzofuran in 95.6% yield over Pd–C in ethanol at room temperature (eq. 12.110).[214]



(12.110)

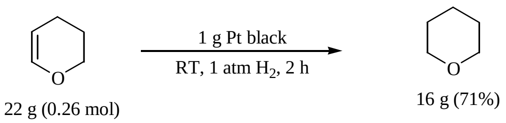
2-Acetylbenzofuran or 2-(1-hydroxyethyl)benzofuran was hydrogenated to 2-(1-hydroxyethyl)-2,3-dihydrobenzofuran in high yields over Raney Ni in ethanol at room temperature and 0.2–0.3 MPa H_2 (eq. 12.111).[215] The selective transformation of 2-acetylbenzofuran to 2-(1-hydroxyethyl)benzofuran was successful over platinum oxide in ethanol (eq. 12.111), while the hydrogenation over a colloidal platinum on Norit catalyst from chloroplatinic acid and platinum oxide gave a mixture of 2-(1-hydroxyethyl)benzofuran, 2-ethylbenzofuran, and their 2,3-dihydro derivatives.



(12.111)

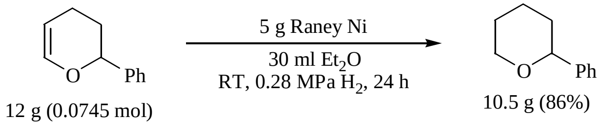
12.2.2 Pyrans, Pyrones, and Related Compounds

Pyrans are hydrogenated to tetrahydropyrans over palladium, platinum, Raney Ni, and rhodium catalysts, and tend to give ring-opened products less than do furans. Although the hydrogenation of 4*H*-pyran itself has rarely been reported, 2,3-dihydro-4*H*-pyran, which would be an intermediate in the hydrogenation of 4*H*-pyran, was hydrogenated to tetrahydropyran over platinum catalyst at room temperature and atmospheric pressure (eq. 12.112)[216]



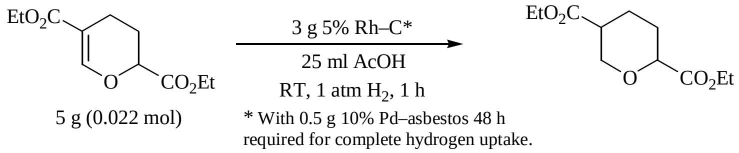
(12.112)

2-Isobutoxy-[217], 2-butyl-,[218] 2-phenyl- (eq. 12.113),[218] and 2-ethoxycarbonyl-[219] substituted 2,3-dihydro-4*H*-pyrans were hydrogenated over Raney Ni at room temperature and elevated hydrogen pressures, although rather long reaction times were required for the 2-isobutoxy and 2-phenyl derivatives.



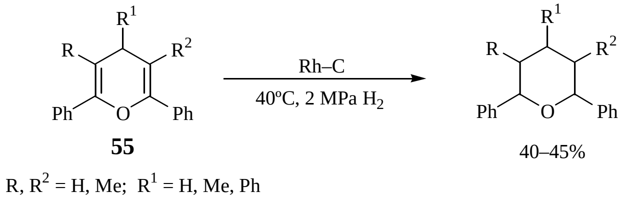
(12.113)

Silberman hydrogenated a number of 2,3-dihydro-4*H*-pyrans substituted in the 2 and 5 positions.[220] With Raney Ni, the hydrogenation conditions varied widely, ranging from ready reactions at room temperature to slow hydrogenations at elevated temperatures and pressures. Hydrogenation of 2,5-diethoxycarbonyl-2,3-dihydro-4*H*-pyran over Raney Ni in ethanol required the conditions of 150°C and 30 MPa H_2. Over rhodium or palladium catalysts in acetic acid, hydrogenation could be effected with ease at room temperature and atmospheric pressure (eq. 12.114), while hydrogenation was considerably slowed in an ethanol solution.



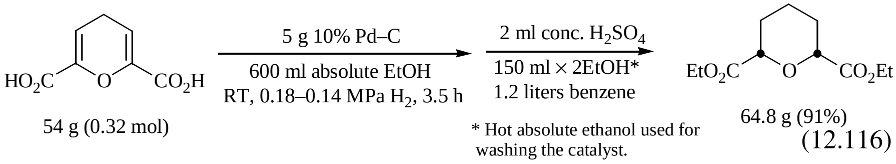
(12.114)

2,6-Diphenyl-4*H*-pyrans (**55**: R, R^2 = H, Me; R^1 = H, Me, Ph) were hydrogenated in the presence of Rh–C at 40°C and 2 MPa H_2 to give 40–45% yields of the tetrahydro derivatives (eq. 12.115).[221] 2,6-Diphenyl-4*H*-pyran (**55**: R = R^1 = R^2 = H) was hydrogenated to 2,6-dicyclohexyltetrahydropyran in the presence of Rh–C.



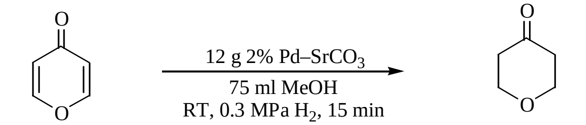
(12.115)

Pyran-2,6-dicarboxylic acid was hydrogenated to *cis*-tetrahydropyran-2,6-dicarboxylic acid in a suspension in ethanol over Pd–C at room temperature (eq. 12.116).[222] Before hydrogenation was completed, the very slightly soluble starting acid had dissolved.



(12.116)

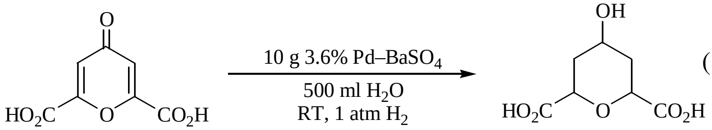
4-Pyrones may be hydrogenated to tetrahydro-4-pyrones or to -4-pyranols. Palladium catalysts appear to be most selective for the hydrogenation to the tetrahydropyrones either in a colloidal state[223,224] or, better, supported on $SrCO_3$.[225] Borsche hydrogenated 4-pyrone, 2,6-dimethyl-4-pyrone, and diethyl chelidonate (diethyl 4-pyrone-2,6-dicarboxylate) to the corresponding tetrahydropyrones in water using colloidal palladium, prepared from gum arabic and palladium chloride, at room temperature and atmospheric hydrogen pressure.[223] Cawley and Plant hydrogenated 4-pyrone with use of Pd–$SrCO_3$ in methanol at room temperature and 0.3 MPa H_2 (eq. 12.117).[225]



(12.117)

11 g (0.11 mol) 8 g (70%)

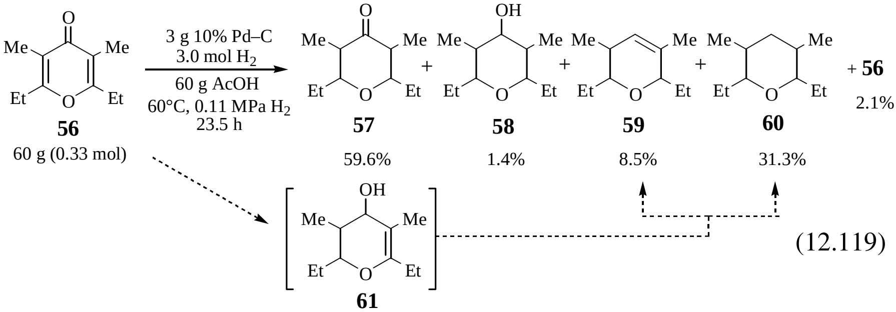
Attenburrow et al., however, observed that none of palladium catalysts (Pd–$BaSO_4$, Pd–C, and colloidal Pd) and Raney Ni were satisfactory for the selective hydrogenation of comanic acid (4-pyrone-2-carboxylic acid), ethyl comanate, chelidonic acid, and diethyl and dimethyl chelidonates to the corresponding tetrahydropyrone derivatives.[226] Nearly 3 mol of hydrogen was taken up in all instances with no evidence of selective hydrogenation. By interrupting the reaction after the absorption of 1 or 2 mol of hydrogen, it was possible to isolate partially hydrogenated products in poor yields. Hydrogenation to tetrahydropyranol derivatives occurs readily over palladium catalysts and thus in the case of chelidonic acid tetrahydro-4-pyranol-2,6-dicarboxylic acid was obtained in 97% yield over Pd–$BaSO_4$ with the uptake of 3 mol of hydrogen (eq. 12.118).



(12.118)

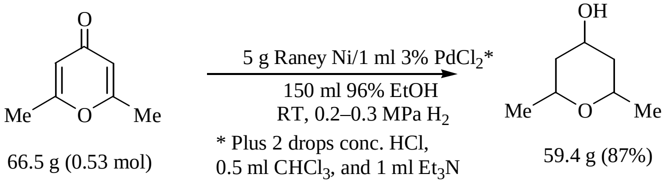
10 g (0.054 mol) 10 g (97%)

Hydrogenation of 2,6-diethyl-3,5-dimethyl-4-pyrone (**56**) over Pd–C in acetic acid was also reported to proceed nonselectively. The products at an uptake of 3 mol of hydrogen consisted, as analyzed by GC, of 59.6% of the tetrahydropyrone **57** and 31.3% of the tetrahydropyran **60** along with a small amount of the dihydropyran **59** and a trace amount of the tetrahydropyranol **58** (eq. 12.119).[227] With a longer reaction time (124 h), 4 mol of hydrogen was taken up and the amount of **60** increased to 48% with the decrease in the amount of **57** to 28%. These results indicated that the tetrahydropyran **60** was formed via the reaction sequence **57** → **58** → **59** → **60**. However, it might be possible that **60**, which appears to have been produced simultaneously with **57** during a rather fast uptake of 3 mol of hydrogen, was formed via intermediates other than **57** and **58**. One possibility of such intermediate is the dihydropyran-4-ol **61**, whose hydroxyl group is expected to be labile toward hydrogenolysis to give **59** and **60** by the electron-releasing ring oxygen.[228]



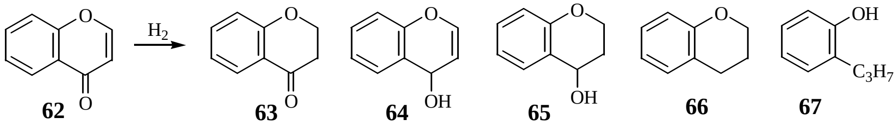
(12.119)

Raney Ni or promoted Raney Ni is an effective catalyst for the hydrogenation of 4-pyrones to the tetrahydropyranols. 4-Pyrone was hydrogenated to tetrahydropyran-4-ol in 75% yield over Raney Ni in ethanol at 100°C and 6 MPa H_2.[229] 2,6-Dimethyl-4-pyrone was hydrogenated over a Raney Ni promoted by $PdCl_2$ in ethanol at room temperature to give the corresponding tetrahydropyranol in high yield (eq. 12.120).[230]

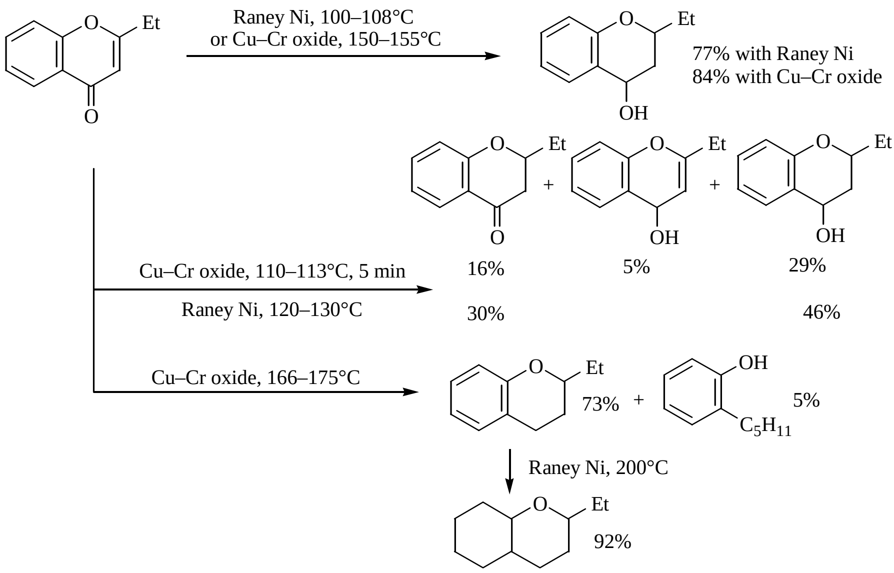


(12.120)

Chromone (benzo-4-pyrone) (**62**) may be hydrogenated to give chromanone (**63**), chromen-4-ol (**64**), chroman-4-ol (**65**), chroman (**66**), and ring-opened product **67** (Scheme 12.29), as well as the products saturated in the benzene ring. 2-Methylchromone was hydrogenated to 2-methylchromanone over Pd–$CaCO_3$ in benzene at room temperature. 2-Methylchromanone was further hydrogenated to 2-methylchromanol over platinum black in benzene.[231] The hydrogenation of 7-hydroxy-2-methylchromone over a palladium black in acetic acid at 20–25°C and 1 atm H_2 led to quantitative formation of 7-hydroxy-2-methylchroman.[232] Mozingo and Adkins hydrogenated 2-ethylchromone with Raney Ni and copper–chromium oxide at various temperatures and 10–20 MPa H_2 (Scheme 12.30).[233] Hydrogenation over Raney Ni at 100–108°C gave 2-ethyl-4-chromanol in 77% yield. 2-Ethylchroman was hydrogenated to 2-

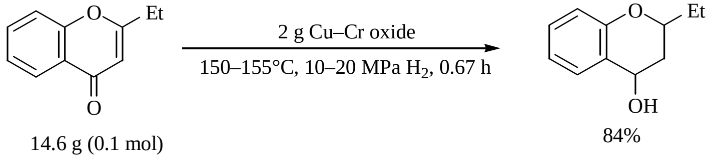


Scheme 12.29 The products to be formed in the hydrogenation of chromone.



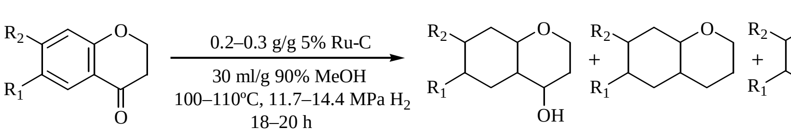
Scheme 12.30 Hydrogenation products of 2-ethylchromone over Raney Ni and copper–chromium oxide (hydrogen pressure 10–20 MPa).

ethylhexahydrochroman in 92% yield at 200°C. Over copper–chromium oxide, 2-ethyl-4-chromanol was obtained in 84% yield at 150–155°C (eq. 12.121). Hydrogenation at 110–117°C gave a mixture of 2-ethylchromanone, 2-ethylchromen-4-ol, and 2-ethyl-4-chromanol. Hydrogenation at 166–175°C gave 73% of 2-ethylchroman and 5% of *o*-pentylphenol. 2-Ethylchromanone was not produced in any considerable amount over copper–chromium oxide since it was readily converted to the alcohol, although the saturated ketone was isolated in a yield of 30% over Raney Ni at 120–130°C.



(12.121)

Hirsch and Schwartzkopf hydrogenated several 4-chromanones over ruthenium catalyst to 1-oxadecalin derivatives.[234,235] The major constituent in each instance (45–95%) of isolated products was a mixture of 4-hydroxy-1-oxadecalins (complex mixtures containing primarily *cis* ring fusions), while significant amounts (5–35%) of 1-oxadecalins and saturated monocyclic alcohols were also isolated (eq. 12.122).[235] It was observed that hydrogenation of the 4-chromanol with R_1 = CO_2Me; R_2 = H resulted in slower ring reduction and almost quantitative benzylic hydrogenolysis.[234]

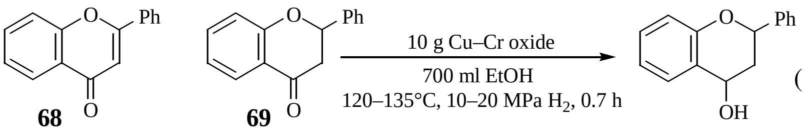


(12.122)

$R_1 = R_2 = H$	95%	Not observed	5%
$R_1 = H$; $R_2 = CO_2Me$	60%	25%*	15%
$R_1 = CO_2Me$; $R_2 = H$	45%	35%†	20%

* Composed of a single *cis*-fused compound by GC.
†Composed of two *cis*-fused compounds in a 4:1 ratio by GC.

Flavone (2-phenylchromone) (**68**) is more labile to hydrogenolysis at the ether linkage than are 2-alkylchromones because it may be considered to be a benzyl-phenyl-type ether. Hydrogenation of flavone over copper–chromium oxide at 140–150°C gave 4-flavanol in a maximum yield of 65% in a very rapid reaction (8 min), while the flavanol was obtained in a yield of 85% in rapid hydrogenation of flavanone (**69**) at 135–145°C or in a yield of 93% in the hydrogenation in a dilute ethanol solution at 120–135°C (eq. 12.123).[233]

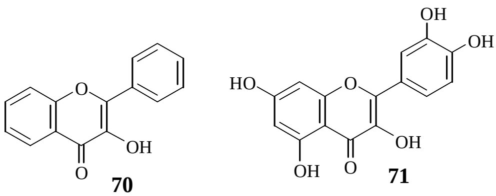


68 **69**

89.6 g (0.4 mol) 93%

(12.123)

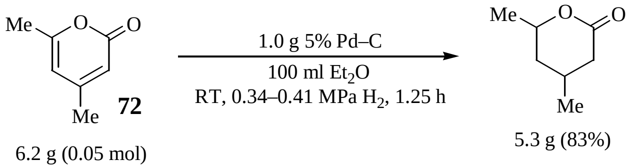
Hydrogenation of flavone or flavanol over copper–chromium oxide at 145–165°C resulted in the formation of *o*-hydroxy-1,3-diphenylpropane as the chief product, which was isolated in yields of about 50%, and in no case flavan was found in a yield greater than 34%. In hydrogenation of flavonol (3-hydroxyflavone) (**70**) over copper–chromium oxide, the catalyst was deactivated rapidly because of a strong acidic character of flavonol, and only 17% of 3,4-dihydroxyflavan was obtained. Probably for a similar reason, quercetin (**71**) was not hydrogenated at all in dioxane over copper–chromium oxide or over Raney Ni, even at 200°C.[233]



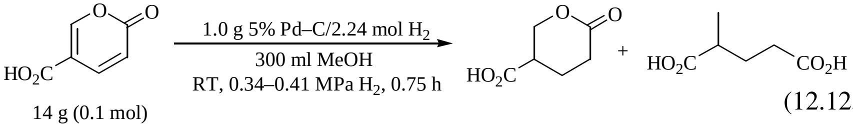
70 **71**

2-Pyrones (coumalins) are hydrogenated readily over platinum oxide or palladium catalysts.[236] Usually 2 equiv of hydrogen are added to 2-pyrones to give the corresponding saturated δ-lactones. However, the hydrogenation may be accompanied by hydrogenolysis to give open-chain derivatives. 4,6-Dimethyl-2-pyrone (**72**) was hy-

drogenated to the saturated lactone in high yield over Pd–C in diethyl ether at room temperature with a hydrogen uptake of 2 equiv (eq. 12.124). Ethyl isodehydroacetate (4,6-dimethyl-5-ethoxycarbonyl-2-pyrone), isodehydroacetic acid (4,5-dimethyl-2-pyrone-5-carboxylic acid), and 6-methoxycarbonyl-2-pyrone were all hydrogenated to the corresponding tetrahydro derivatives with the uptake of 2 equiv of hydrogen over Pd–C in ether or methanol. However, coumalic acid (2-pyrone-5-carboxylic acid) was hydrogenated most rapidly absorbing 2.24 equiv of hydrogen, and 2-methylglutaric acid was identified as a hydrogenolysis product (eq. 12.125).[236]

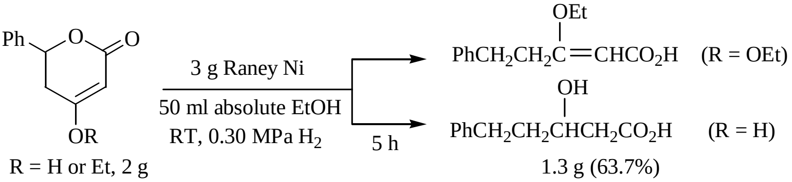


(12.124)



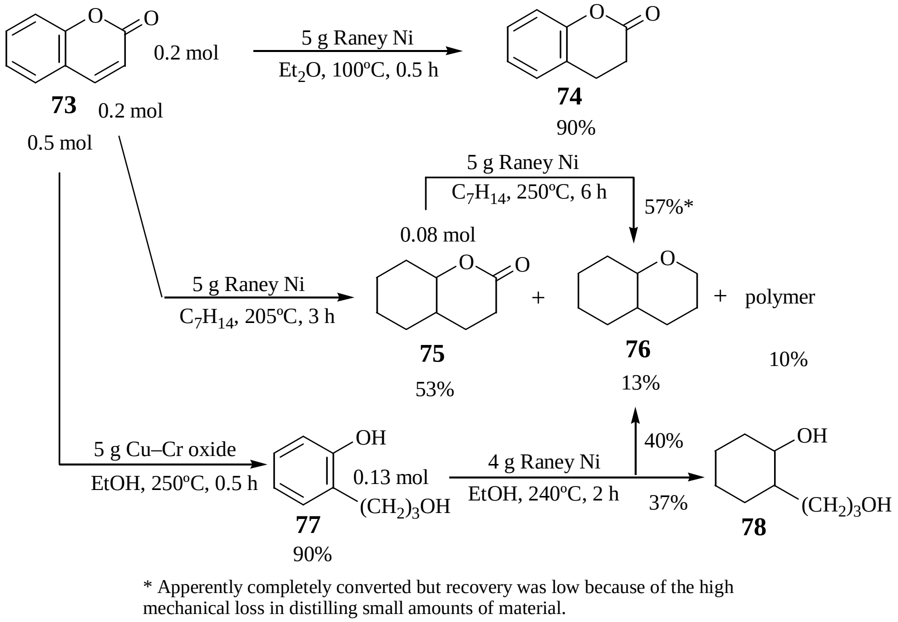
(12.125)

Hydrogenolysis of 2-pyrone derivatives to give open-chain products occurs especially readily when phenyl group is substituted in the 6 position.[237,238] 4-Ethoxy- and 4-hydroxy-6-phenyl-5,6-dihydro-2-pyrones were hydrogenated to give 3-ethoxy-5-phenyl-2-pentenoic acid and 3-hydroxy-5-phenylvaleric acid, respectively, over Raney Ni at room temperature and 0.3 MPa H_2 (eq. 12.126).[237]



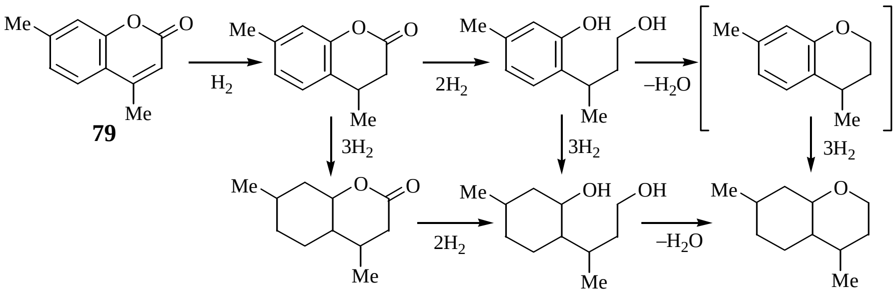
(12.126)

Coumarin (2*H*-1-benzopyran-2-one) (**73**) was hydrogenated to dihydrocoumarin **74** in 90% yield over Raney Ni in ether at 100°C.[239] Dihydrocoumarins were also obtained by the hydrogenation of corresponding coumarins over palladium catalysts.[240] At 200–250°C over Raney Ni, the main reactions of coumarin were saturation of the benzenoid ring, giving the octahydrocoumarin **75**, and conversion of the lactone to the cyclic ether, hexahydrochroman **76**. Compound **75** was obtained in 53% yield, along with 13% of **76**, by carrying out the hydrogenation in methylcyclohexane at 205°C and interrupting the reaction before the absorption of hydrogen ceased. Higher yields (up to 35%) of **76** were obtained by a longer reaction period at 250°C. Hydrogenation of coumarin over copper–chromium oxide in ethanol at 250°C gave 3-(*o*-hydroxyphenyl)-1-propanol (**77**) in 90% yield, although at 140–160°C the initial formation of dihydrocoumarin **74** was shown by the corresponding pressure drop. The hydrogenation of **77** in ethanol over Raney Ni at 240°C gave hexahydrochroman **76**



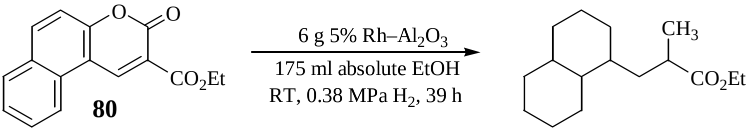
Scheme 12.31 Products from hydrogenation of coumarin and related compounds over Raney Ni and copper–chromium oxide (H_2 pressure: 10–20 MPa).

and 3-(2-hydroxycyclohexyl)-1-propanol (**78**).[240] The hydrogenation products of coumarin and related compounds over Raney Ni and copper–chromium oxide are summarized with the reaction conditions shown in Scheme 12.31. Further studies by de Benneville and Connor on the hydrogenation of 4,7-dimethylcoumarin (**79**) indicated that both phenolic alcohols and saturated lactones are intermediates in the conversion of coumarins to hexahydrochromans over Raney Ni, as shown in Scheme 12.32.[241] Both



Scheme 12.32 Hydrogenation pathways of 4,7-dimethylcoumarin over Raney Ni leading to the formation of hexahydro-4,7-dimethylchroman.

pathways to hexahydrochromans involve the ring closure of the dihydroxy compounds that are generally produced by the reactions over copper–chromium oxide. Hydrogenation of ethyl 5,6-benzocoumarin-3-carboxylate (**80**) over a rather large amount of Rh–Al_2O_3 in ethanol at room temperature and a low hydrogen pressure resulted in extensive hydrogenolysis of the lactone to give ethyl 3-(1-decalyl)-2-methylpropionate (eq. 12.127).[242]



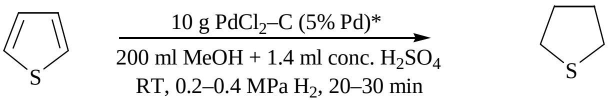
(12.127)

4.0 g (0.015 mol)

3.3 g (89%) (crude)
1.55 g (42%) (purified)

12.3 *S*-HETEROCYCLES

The sulfur-containing compounds are generally strong poisons for common metal catalysts, especially when the sulfur atoms in the compounds are unshielded.[243] Therefore, the use of oxide or sulfide catalysts is usually preferred, although rather vigorous conditions are required for these catalysts. Nickel catalysts, in particular Raney Ni, have a strong affinity for sulfur compounds, and tend to remove the sulfur atom from the compounds.[244] Mozingo et al. hydrogenated some divalent sulfur-containing compounds under mild conditions using large amounts of Pd–C or Pd–$BaSO_4$ in the presence or absence of a mineral acid.[245] Thus, thiophene (eq. 12.128) and 5-(2-thienyl)valeric acid were hydrogenated to the corresponding tetrahydro compounds over Pd–C in methanol in the presence of sulfuric acid at room temperature and a few atmospheres of hydrogen.



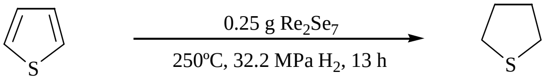
(12.128)

0.42 g (5 mmol)

* Prereduced before the addition of substrate and sulfuric acid.

1.26 g (71%) as $HgCl_2$ adduct

Thiophene was also hydrogenated to tetrahydrothiophene over rhenium heptasulfide (Re_2S_7) at 230–260°C[246] or rhenium heptaselenide (Re_2Se_7) at 250°C and at pressures greater than 30 MPa H_2 (eq. 12.129),[247] without accompanying hydrogenolysis of the carbon–sulfur bond that occurred extensively over molybdenum sulfide.[246]



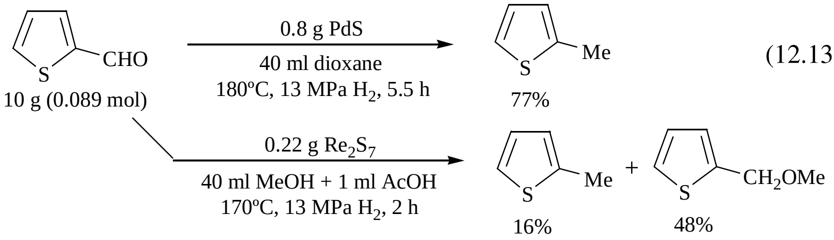
(12.129)

8.4 g (0.1 mol)

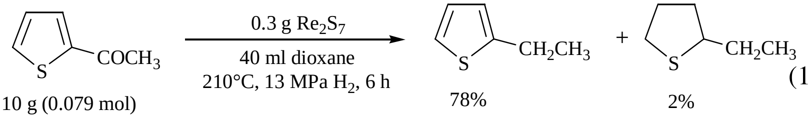
100%

Thiophene-2-carboxaldehyde was hydrogenated to 2-methylthiophene in 77% yield over a PdS catalyst in dioxane at 180°C and 13 MPa H_2, while hydrogenation of the

aldehyde over Re_2S_7 in methanol at 170°C and 13 MPa H_2 was accompanied by the formation of 48% of 2-methoxymethylthiophene along with 16% of 2-methylthiophene (eq. 12.130). Hydrogenation of 2-acetylthiophene over Re_2S_7 in dioxane at 210°C gave 78% of 2-ethylthiophene and 2% of 2-ethyltetrahydrothiophene (eq. 12.131).[248] The formation of the tetrahydro compound increased to 44% in the hydrogenation at 270°C.

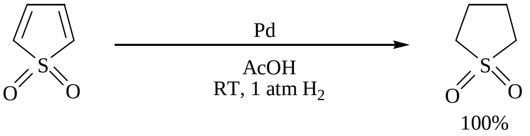


(12.130)



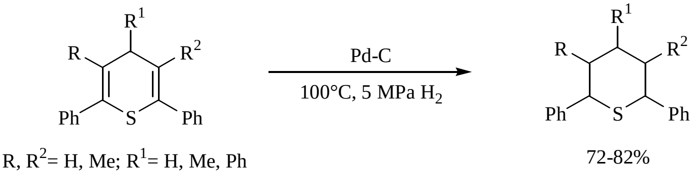
(12.131)

Thiophene 1,1-dioxide with a shielded sulfur atom was hydrogenated without difficulty to the tetrahydro derivative, sulfolane, over palladium catalyst in acetic acid at room temperature and atmospheric hydrogen pressure (eq. 12.121).[249]



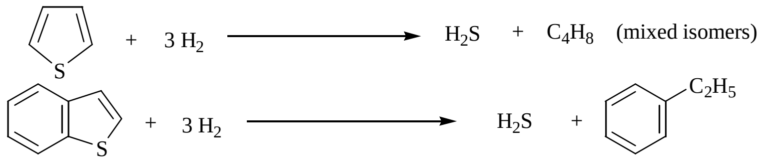
(12.132)

2,6-Diphenylthiopyrans were hydrogenated to the corresponding tetrahydro derivatives in the presence of Pd–C at 100°C and 5 MPa H_2 (eq. 12.133).[221]



(12.133)

Hydrogenation of thiophene and benzothiophene over metal oxide or sulfide catalyst at high temperature (300–400°C) and low hydrogen pressure (usually 0.1–0.7 MPa) leads to the hydrogenolyzed products, butenes and ethylbenzene, along with hydrogen sulfide (Scheme 12.33), a reaction that is an important process in petroleum refinery known as *hydrodesulfurization*.[250] The most commonly used catalyst is a mixture of cobalt and molybdenum oxides on γ-Al_2O_3, which is sulfided before use. It is of interest to note that the ring in thiophene is not hydrogenated before the sulfur is re-



Scheme 12.33 Hydrodesulfurization of thiophene and benzothiophene.

moved, whereas the sulfur in benzothiophene is removed after the thiophene ring is hydrogenated to the 2,3-dihydro derivative.[250]

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CHAPTER 13

Hydrogenolysis

Catalytic hydrogenolysis involves the cleavage with hydrogen of various bonds such as C–C, C–O, C–N, C–S, and C–X. Some hydrogenations of unsaturated groups such as nitro to amino ($R–NO_2 + 3H_2 \rightarrow R–NH_2 + H_2O$) or esters to alcohols ($RCO_2R' + 2H_2 \rightarrow RCH_2OH + R'OH$) involve hydrogenolyses that accompany the hydrogenations. This chapter deals principally with the reactions associated with a direct cleavage of σ bonds in the field of organic synthesis. Catalytic hydrogenolysis is an important reaction involved in the fuel or petroleum industry as in coal liquefaction, hydrocracking, hydrodesulfurization, and hydrodenitrogenation.[1]

13.1 HYDROGENOLYSIS OF CARBON–OXYGEN BONDS

13.1.1 Alcohols and Ethers

In general, the hydrogenolysis of carbon–oxygen bonds in saturated alcohols and ethers is not easy under conditions employed for the usual hydrogenations and requires rather drastic conditions. For example, the hydroxyl group in primary and secondary alcohols is resistant to hydrogenolysis over nickel and copper–chromium oxide at temperatures below 250°C unless the hydroxyl group is activated by some other groups.[2] Similarly, dialkyl ethers are stable toward hydrogenolysis over nickel catalysts at temperatures below ~250°C. At 250°C, however, hydrogenolysis of a primary alcohol according to the equation $RCH_2OH + 2H_2 \rightarrow RH + CH_4 + H_2O$ occurs over nickel catalyst under 10–20 MPa H_2. Secondary alcohols also undergo hydrogenolysis under these conditions, but in this case the reaction involves only the cleavage of a carbon–oxygen bond shown by the equation $R_2CHOH + H_2 \rightarrow R_2CH_2 + H_2O$.[3] As an example, cylohexanol (41 g, 0.41 mol) reacted with hydrogen over Raney Ni (7 g) at 250°C to give 48% of cyclohexane together with 50% of unreacted cyclohexanol in 5 h. 2-Octanol, however, gave only 15% of octane under similar conditions.

1,3-Glycols are considerably less stable than 1,2- and 1,4-glycols.[4] Thus, cyclohexane-1,3-diol was almost quantitatively converted to cyclohexanol over copper–chromium oxide at 200°C and 17.5 ± 3.5 MPa H_2, while the 1,2 isomer gave only 20% of cyclohexanol even at 250°C for a longer reaction time and the 1,4 isomer was quite stable and recovered unchanged at 250°C.[5] Similarly, glycerol was converted to propane-1,2-diol in 85% yield and propane-1,3-diol to 1-propanol in 94% yield at 250°C. Butane-1,3-diol gave a mixture of 56% of 2-butanol and 32% of 1-butanol, indicating that the hydroxy group on the primary carbon was removed more easily than that on the secondary carbon.

Unsaturated groups, such as vinyl, phenyl, furyl, pyrryl, carbonyl, and alkoxycarbonyl, have a marked effect in labilizing the carbon–oxygen linkage. Hydrogenolysis of allyl and benzyl compounds will be considered later. β-Hydroxy and β-alkoxy ketones and carboxylic acids or esters are especially labile to hydrogenolysis, particularly, over those catalysts that do not contain alkaline substances. An extensive hydrogenolysis in the hydrogenation of resorcinol over palladium catalyst is probably due to the fact that 3-hydroxycyclohexanone formed as an intermediate is very labile to hydrogenolysis. Similarly, 3-methoxycyclohexanone was hydrogenated quantitatively to cyclohexanone over palladium black even at room temperature. The extremely facile formation of cyclohexanone in these cases probably takes place via prior elimination of the hydroxy or methoxy group as water or methanol, respectively, to give 2-cyclohexen-1-one, an α,β-unsaturated ketone, followed by hydrogen addition to the double bond. This type of elimination may be greatly promoted by the adsorbed ionized hydrogen on palladium[6] and may be depressed by alkaline substances on the catalyst surface. The tendency toward hydrogenolysis decreases sharply with γ-hydroxy and γ-alkoxy ketones, such as 4-hydroxy- and 4-methoxycyclohexanones.[7]

Acetals seldom are usually hydrogenolyzed so readily under mild conditions. However, Howard and Brown, Jr. found that acetals may be hydrogenolyzed to give the corresponding ethers and alcohols over rhodium catalyst in the presence of acid. Acetals of secondary alcohols react faster than those of primary alcohols (eq. 13.1).[8]

$$\underset{0.2\ \text{mol}}{R_2C(OR')_2} \xrightarrow[\text{conc. HCl (1 drop)},\ 25^\circ\text{C, 0.24–0.41 MPa } H_2]{0.2\text{ g }5\%\text{ Rh–Al}_2\text{O}_3} R_2CH{-}OR' \quad + \quad R'OH \qquad (13.1)$$

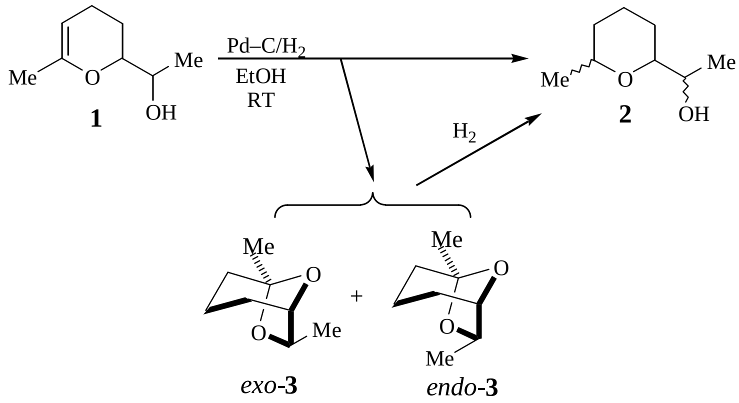
Acetal	Time (h)	H_2 consumed (% of theory)
R = Me, R' = Bu	4	34
R = Me, R' = *i*-Pr	1	97

Palladium was about half as active as rhodium, and platinum and ruthenium were almost inactive for the hydrogenation of isopropenyl methyl ether. Since these metals showed the same order of activity for the hydrogenolysis of acetone diisopropyl acetal, it has been suggested that the dissociation of the acetal to unsaturated ether and alcohol to form an equilibrium mixture (eq. 13.2) constitutes the first step in the hydrogenolysis of acetals. Hydrogenation then removes the unsaturated ether and allows further conversion of the acetal to the unsaturated ether.

$$R_2CHCR'(OR'')_2 \overset{H^+}{\rightleftharpoons} R_2C{=}CR'(OR'') \quad + \ R''OH \qquad (13.2)$$

This mechanism was supported by the experimental facts that the acetals of primary alcohols were less completely converted than those of secondary alcohols, because the equilibrium shown in eq. 13.2 will be less favorable for the formation of unsaturated ether when the alkoxy groups are primary. Acetals may also be hydrogenolyzed in a neutral solvent over a palladium catalyst not containing alkali.[9,10]

Lipkowitz et al. observed that the hydrogenation of cyclic enol ether **1** to **2** over a 10% Pd–C in ethanol was accompanied by the formation of bicyclic acetals of the formula **3**, of which the *endo* isomer was hydrogenolyzed to give **2** much more rapidly



Scheme 13.1 Formation and hydrogenolysis of bicyclic acetals in the hydrogenation of a cyclic enol ether **1**.

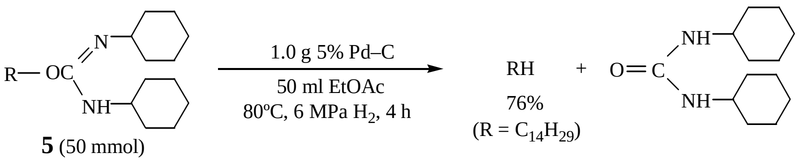
than the *exo* isomer (Scheme 13.1).[10] This result was explained by a steric effect of the *exo* methyl group to hinder the hydrogenolysis of *exo*-**3** by an attack of hydrogen from the catalyst surface.[11] The carbon–oxygen bond in trialkylalkoxysilane, an alkyl trialkylsilyl ether, may be hydrogenolyzed over nickel catalysts at high temperatures and pressures[12] or over Pd–C at room temperature and atmospheric pressure.[13] Thus benzyloxytrimethylsilane (**4**) is hydrogenolyzed over Pd–C in cyclohexane to give almost quantitative yield of toluene and hexamethyldisiloxane (eq. 13.3).

$$2\ PhCH_2{-}OSiMe_3 \xrightarrow[\text{20 ml cyclohexane; 25°C, 1 atm } H_2\text{, 20 min}]{\text{1 g 10\% Pd-C}} 2\ PhCH_3 + Me_3SiOSiMe_3 \qquad (13.3)$$

4 (0.01 mol) — almost quantitative

Alkoxytrimethylsilanes such as the ethoxy, isopropoxy, and *t*-butoxysilanes were also hydrogenolyzed under the same conditions, although the reaction could not be monitored by hydrogen uptake when the hydrocarbon products were gaseous. Aryloxytrimethylsilanes, such as 4-(trimethylsilyl)phenoxytrimethylsilane, were hydrogenated to the corresponding cyclohexyloxy derivatives over Raney Ni at elevated temperature and pressure; the Ar–OSi bond remained intact.

Hydrogenolysis of eq. 13.4 allows an alcohol to be transformed into the hydrocarbon. The ether **5**, obtained by the reaction of *N*,*N*′-dicyclohexylcarbodiimide with an alcohol, is also susceptible to hydrogenolysis over Pd–C under mild conditions (eq. 13.4).[14]

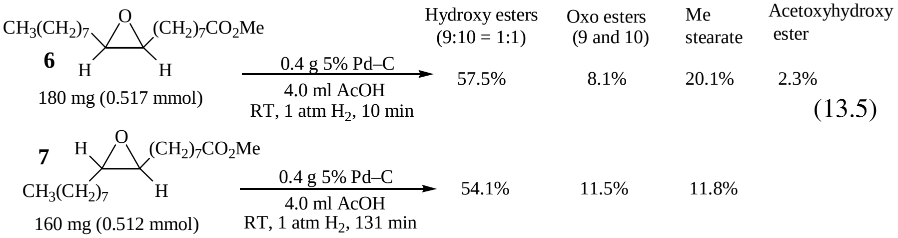


(13.4)

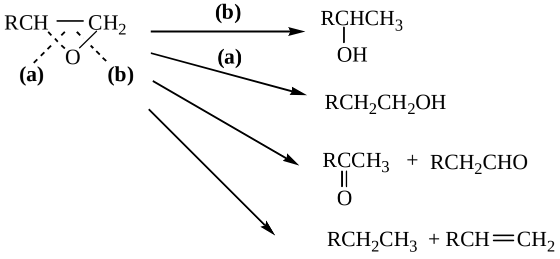
5 (50 mmol)

13.1.2 Epoxy Compounds

In general, epoxides or oxiranes are labile to hydrogenolysis under rather mild conditions because of a strong tendency to release their ring strain. The hydrogenolysis of unsymmetric epoxides may afford two different alcohols by the C–O bond that undergoes the reaction. Further, isomerization to carbonyl compounds and formation of deoxygenated compounds may accompany the formation of the alcohols (Scheme 13.2). Fore and Bickford observed that the hydrogenolysis of *cis*-6,7-epoxyoctadecanoic acid, which was unsuccessful over either Raney Ni, Adams platinum, or 5% Pd-$CaCO_3$ in ethanol at room temperature and 0.14–0.21 MPa H_2, was readily effected with use of 10% Pd–C under the same conditions.[15] Usually the theoretical amount of hydrogen was absorbed and 6- and 7-hydroxyoctadecanoic acids were formed in approximately equimolar quantities. However, in one experiment, the reaction was abnormally rapid and completed in 12 min, compared to several hours in usual hydrogenations, with the absorption of 1.3 equiv of hydrogen. The product of the rapid hydrogenation was found to contain up to 40% of stearic acid along with the two hydroxy acids in nearly equimolar amounts.[15] Howton and Kaiser, Jr. studied the hydrogenation products of 9,10-epoxystearates over Pd–C in acetic acid by means of silicic column chromatography.[16] Contrary to the results of earlier studies,[17] it was shown that 9- and 10-hydroxystearates were formed in equal amounts from both the *cis*- and *trans*-epoxy esters **6** and **7**, together with smaller amounts of stearate and oxostearates. It is of interest that the *cis* ester was hydrogenated 10 times as rapidly as the t*rans* isomer and gave a larger amount of stearate (eq. 13.5).



(13.5)



Scheme 13.2 Possible products of hydrogenolysis of an unsymmetric epoxide.

Newman et al. found that the hydrogenolysis of 1,2-epoxydecane over Raney Ni in ethanol at 150°C and 6.2 MPa H_2 gave an approximately 9:1 mixture of 1- : 2-decalol, while the ratio was reversed to 1: 10–20 when the epoxide was hydrogenated with addition of a small amount of sodium hydroxide.[18] In contrast, the course of the hydrogenolysis of styrene oxide was not affected by acid or alkali; 2-phenylethanol was always formed preferentially. Mitsui et al. investigated the hydrogenation of 1,2-epoxydecane in detail with nickel wire, Raney Ni, palladium wire, and Pd–C as catalysts in ethanol at 150°C and 6 MPa H_2.[19] The results summarized in Table 13.1

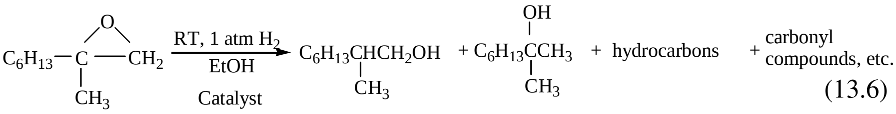
TABLE 13.1 Effects of Additives on the Hydrogenation of 1,2-Epoxydecane over Nickel and Palladium Catalysts[a,b]

			Product (%)				
Catalyst	Amount (g)	Additive ($\times 10^{-3}$ mol)	Epoxydecane	Isomerized Product[c]	Decanol	(1- : 2-)[d]	Other Products[e]
Ni wire	1.3	—	1	0	91	(65 : 35)	8
Raney Ni	0.4[f]	—	0	0	98	(62 : 38)	2
		NaOH, 0.4	0	0	83	(11 : 89)	17
		LiCl, 0.4	0	0	94	(52 : 48)	6
		NaCl, 0.4	0	0	94	(51 : 49)	6
		KCl, 0.4	0	0	93	(42 : 58)	7
		RbCl, 0.4	2	Trace	80	(39 : 61)	18
		CsCl, 0.4	8	2	70	(29 : 71)	20
		NaBr, 0.4	0	0	99	(39 : 61)	1
		NaBr, 1.0	0	0	99	(28 : 72)	1
		KBr, 0.4	0	0	95	(32 : 68)	5
		KI, 0.4	1	Trace	97	(6 : 94)	2
		Pyridine, 0.4	0	0	96	(62 : 38)	4
		Piperidine, 0.4	0	0	92	(57 : 43)	8
		Et_2NH, 0.4	0	0	87	(62 : 38)	13
		NH_3, 0.4	0	0	96	(55 : 45)	4
5% Pd–C A[g]	0.2	—	2	1	30	(35 : 65)	67
		NaOH, 1.0	5	Trace	90	(12 : 88)	5
5% Pd–C B[h]	0.2	—	1	1	82	(43 : 57)	16
		NaOH, 1.0	0	1	31	(3 : 97)	68
		CsCl, 1.0	14	3	47	(11 : 89)	36
		KI, 1.0	5	1	93	(5 : 95)	1

[a]Data of Mitsui, S.; Imaizumi, S.; Hinoto, Y. *Nippon Kagaku Zasshi* **1965**, *86*, 225. Reprinted with permission from Chemical Society of Japan.
[b]1,2-Epoxydecane (0.01 mol) was hydrogenated in 50 ml ethanol at 150°C and an initial hydrogen pressure of 6 MPa for 5 h.
[c]Apparently aldehyde and ketone.
[d]Ratio of 1-decalol : 2-decalol.
[e]Apparently solvolysis products.
[f]Amount of wet catalyst.
[g]Acidic Pd–C prepared by reduction of $PdCl_2$ with hydrogen in the presence of active carbon.
[h]Basic Pd–C prepared from $PdCl_2$ by reduction with formaldehyde and sodium hydroxide in the presence of active carbon.

indicate that over well-washed Raney Ni or nickel wire 1-decalol is formed in excess, while formation of 2-decalol increases in the presence of NaOH, CsCl, and KI. It is noted that the highest selectivity to 2-decalol (94%) was obtained in the presence of KI, rather than in the presence of NaOH (89%). Over palladium catalysts, 2-decalol was always produced in excess, although considerable amounts of solvolysis products were formed by catalysts and additives. Similar to the cases with Raney Ni, the selectivity to 2-decalol increased further in the presence of NaOH, CsCl, and KI. Particularly, Pd–C A with NaOH and Pd–C B with KI afforded high yields of 2-decalol (79 and 88%, respectively), accompanied by only small amounts of byproducts. Sajiki et al. obtained 2-decalol in a high selectivity of more than 98% with an 81% yield in the hydrogenolysis of 1,2-epoxydecane over a 10% Pd–C treated with ethylenediamine[20] in methanol at room temperature and 0.1–0.5 MPa H_2.[21]

Hydrogenation of 1,2-epoxy-2-methyloctane (**8**), carrying the epoxy group attached to a primary carbon and a tertiary carbon, gives selectively the primary alcohol over Raney Ni, while over palladium hydroxide catalyst, the tertiary alcohol is formed in 85% selectivity. In the presence of sodium hydroxide the tertiary alcohol was obtained quantitatively over the palladium catalyst by depressing the formation of other products such as hydrocarbons and carbonyl compounds (eq. 13.6).[22]

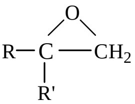


(13.6)

8

Catalyst	$C_6H_{13}CH(CH_3)CH_2OH$	$C_6H_{13}C(OH)(CH_3)CH_3$	hydrocarbons	carbonyl compounds, etc.
Raney Ni	50%	Trace	34%	16%*
Raney Ni/NaOH	31	64%	5	-
$Pd(OH)_2$	2.7	14.3	77	6
$Pd(OH)_2$/NaOH	Trace	100	Trace	0

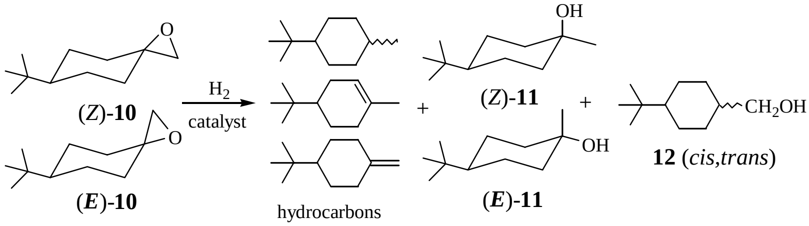
* Solvolysis products.



9

Results on the hydrogenation of unsymmetric epoxyalkanes **9**, R = C_2H_5, R′ = H or CH_3; R = C_6H_{13} or $C_{10}H_{21}$, R′ = H, over transition metals in cyclohexane at room temperature and atmospheric pressure, indicated that the tendency of catalyst metals to form the primary alcohol increased in the following order: Pt < Pd < Os < Ru < Ni < Co. The selectivity to the primary alcohol was 99–100% over cobalt catalyst, while over platinum the selectivity to secondary or tertiary alcohol was always 100%. In the hydrogenation of an optically active epoxyalkane (**9**: R = C_2H_5, R′ = CH_3), the stereoselectivity in the formation of the primary alcohol decreased in the order: Co > Ni > Ru > Pd > Os. Over cobalt and nickel catalysts, the primary alcohol with retention of the configuration was produced in excess, while over palladium and osmium, the alcohol with inversed configuration was formed in excess.[23]

In the hydrogenation of (*Z*)- and (*E*)-4-*t*-butylmethylenecyclohexane oxides [(*Z*)- and (*E*)-**10**] in ethanol at room temperature and 9.8 MPa H_2 (eq. 13.7 and Table 13.2), platinum was highly selective for the formation of the tertiary alcohol **11** with (*Z*)-**10**, while with (*E*)-**10** the primary alcohol **12** was formed in excess. Over the other transition metals, the tendency to form the primary alcohol was much greater, particularly with (*E*)-**10**, where selectivity to the primary alcohol was quantitative over Raney Co, Raney Ni, ruthenium, and palladium. In general, selectivity to produce the primary alcohol over the tertiary alcohol increased in the order Pt < < Pd < Ru, Os, Raney Ni < Raney Co. In the case of Pd the major products were hydrocarbons that amounted to 86% with (*Z*)-**10** and 94% with (*E*)-**10**. The amounts of hydrocarbons formed were similarly greater with (*E*)-**10** than with (*Z*)-**10** over the other metals as well. Over Raney Co the primary alcohol that retained the configuration was formed predominantly, while over osmium the primary alcohol with inversed configuration was produced in excess.[24]



(13.7)

Accrombessi et al. studied the hydrogenolysis of various epoxycyclohexanes over 10% Pd–C in different solvents at 20° and 1 atm H_2.[25] The hydrogenolysis of both *trans*- and *cis*-1,2-epoxy-4-*t*-butylcyclohexanes (**13** and **14**) occurs to give preferentially the axial alcohols by apparent *trans* addition of hydrogen (eq. 13.8), as evidenced by deuterolysis.

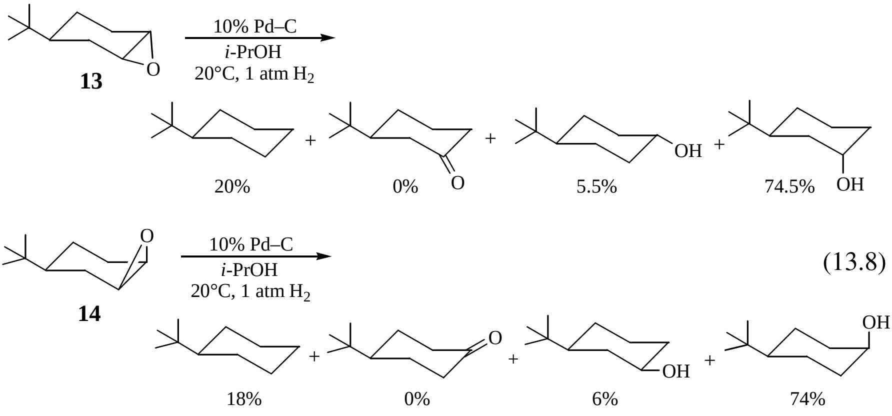
TABLE 13.2 Hydrogenation of (*Z*)- and (*E*)-4-*t*-Butylmethylenecyclohexane Oxides over Transition Metals[a,b]

	Hydrogenation of (*Z*)-**10**					Hydrogenation of (*E*)-**10**				
	Product Ratio					Product Ratio				
Catalyst	HC[c]:	(*Z*)-**11**	: **12**	(*Z*)-**11**:**12**	*t*-12:*c*-**12**	HC[c]:	(*E*)-**11**	: **12**	(*E*)-**11**:**12**	*t*-**12**:*c*-**12**
Raney Co	27	0	73	0:100	78:22	51	0	49	0:100	27:73
Raney Ni	12	13	75	15:85	61:39	13	0	87	0:100	50:50
Ru	30	5	62	7:93	45:55	35	0	65	0:100	57:43
Pd	86	8	6	57:43	62:38	94	0	6	0:100	87:13
Os	6	19	75	20:80	15:85	13	6	81	7:93	80:20
Pt	3	91	6	94:6	52:48	47	21	32	40:60	62:38

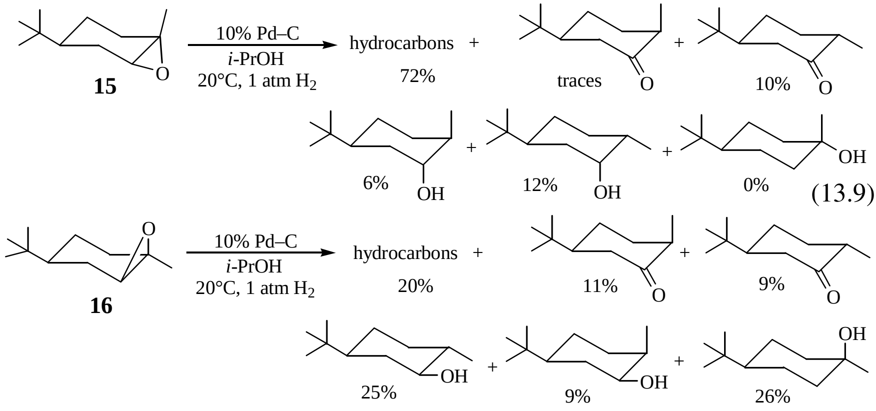
[a]Data of Yashima, H.; Ishiyama, J.; Senda, Y.; Imaizumi, S. Preprints 1B12, Tohoku Regional Meeting of 7 Chemical Associations, Oct. 1984, Yamagata, Japan. Reprinted with permission from Chemical Society of Japan.

[b]Hydrogenated in ethanol at room temperature and 9.8 MPa H_2. For the notations of compounds, see eq. 13.7.

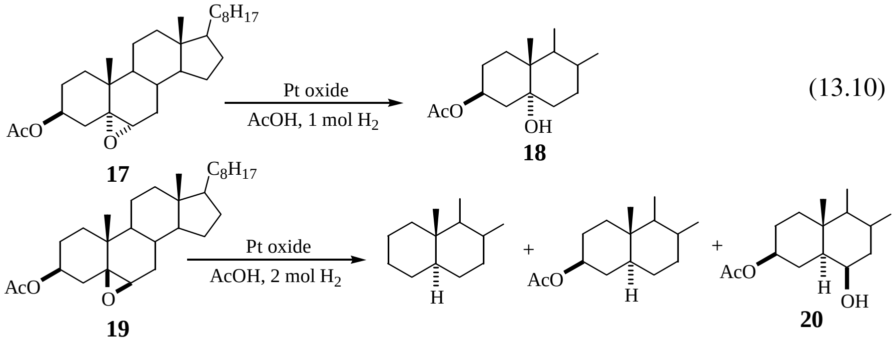
[c]Hydrocarbons.



If one epoxide carbon carries a methyl group as in **15** and **16**, C–O bond cleavage at the more substituted carbon leading to equatorial alcohols becomes competitive with preferential formation of axial alcohols. The products, however, are affected greatly by conformational and steric factors. The formation of hydrocarbons is the major reaction with **15**, while with **16** the hydrocarbons are formed in much lesser amount (20%) and the alcohols constitute the major product (60%) (eq. 13.9).



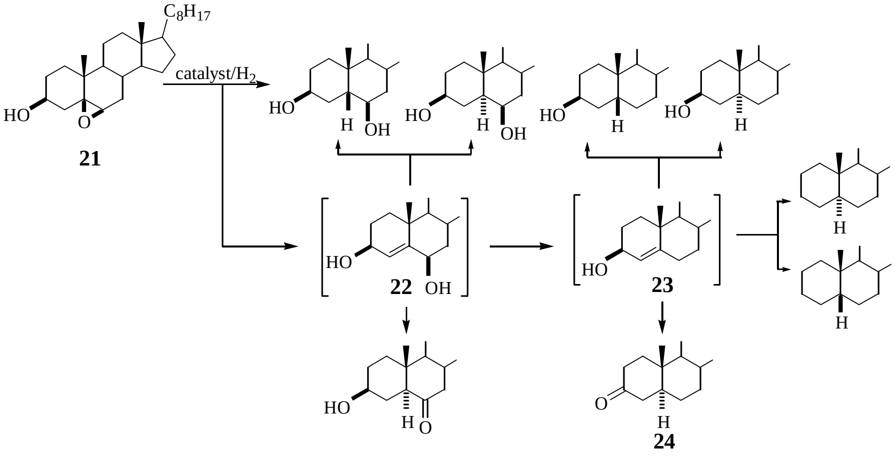
Hydrogenation of 3β-acetoxycholest-5-ene α-oxide (**17**) over Adams platinum oxide in acetic acid gives the axial 5α-ol derivative **18** with uptake of 1 equiv of hydrogen, while hydrogenation of the corresponding β-oxide **19** proceeds much faster and affords large quantities of 5α-cholestane and 3β-acetoxy-5α-cholestane, along with the axial 6β-ol derivative **20**, with uptake of 2 equiv of hydrogen (eq. 13.10).[26,27] Thus, the loss of oxygen function takes place in the 5,6-β-epoxy group as well as in the 3β-acetoxy group with **19**. Nishimura et al. investigated the hydrogenation of cholesterol β-oxide (**21**) in acetic acid, using platinum, palladium, and 7:3 rhodium–platinum oxides of Adams type, in comparison with the hydrogenation of cholest-4-ene-3β,6β-



(13.10)

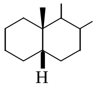
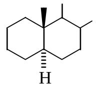
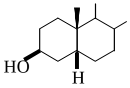
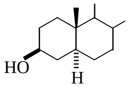
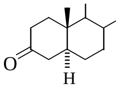
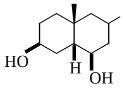
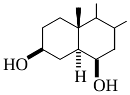
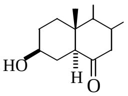
diol (**22**). The product compositions, analyzed by means of GC, are summarized in Table 13.3.[28]

The extensive loss of 3β-hydroxy group over platinum and palladium as well as the formation of 5β compounds, although in small amounts, over all the metals could be best explained by assuming that the oxide **21** was isomerized to the allylic alcohol **22** during hydrogenation, and the **22** formed was further hydrogenated to give cholestanes, cholestanols, and cholestanediols of both 5α and 5β series, as illustrated in Scheme 13.3. Such isomerization of an epoxide to an allylic alcohol is known to occur in the presence of acid.[29] The direct attack of hydrogen from the β face will be strongly hindered with the oxide **21**, and it will be more probable that the hydrogenation via **22** may lead to the formation of 5β compounds.[28,30] The isomeriztion assumed above has been supported by the fact that a significant amount of 5α-chloestan-3-one (**24**) is formed on palladium, since the precursor of **24** is considered to be an allylic alcohol **23**. The isomerization of **23** to **24** may also occur over platinum and rhodium–platinum to lesser extents than over palladium. However, the carbonyl compounds



Scheme 13.3 Hydrogenation and hydrogenolysis pathways of cholesterol β-oxide.

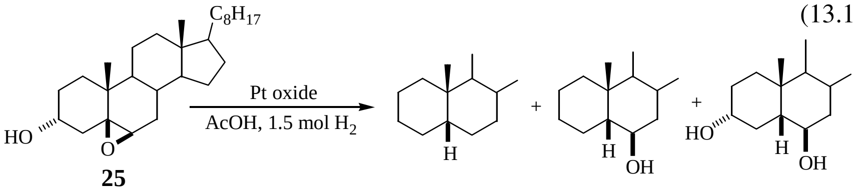
TABLE 13.3 Products of the Hydrogenation of Cholesterol β-Oxide and Cholest-4-ene-3β,6β-diol (mol%)[a]

	Compound Hydrogenated				
	Cholesterol β-oxide[b]			Cholest-4-ene-3β,6β-diol[c]	
Product	Pt	Pd	7 : 3 Rh–Pt	Pt	7 : 3 Rh–Pt
	3	14	Trace	5	Trace
	28	32	3	43	2
	11	7	6	13	4
	23	27	16	28	9
	—	20	—	—	—
	6	—	26	5	46
	30	—	48	6	39
	—	Trace	—	—	—

[a]Data of Nishimura, S.; Shiota, M.; Mizuno, A. *Bull. Chem. Soc. Jpn.* **1964**, *37*, 1207. Reprinted with permission from Chemical Society of Japan.
[b]The compound (200 mg, 0.5 mmol) was hydrogenated over 50 mg of catalyst in 30 ml of AcOH at room temperature and atmospheric hydrogen pressure.
[c]The compound (70 mg, 0.17 mmol) was hydrogenated over 30 mg of Pt oxide in 15 ml AcOH at room temperature and atmospheric hydrogen pressure. The hydrogenation over 7 : 3 Rh–Pt oxide was carried out under similar conditions (Nishimura, S.; Mori, K. *Bull. Chem. Soc. Jpn.* **1963**, *37*, 318).

formed may be further hydrogenated to the corresponding alcohols over these catalysts. Plattner et al.[31] suggested that cholestanes and cholestanols might have been produced via 5β-cholestan-3β,5-diol. However, this pathway will not be probable, since the 3β,5β-diol was recovered unchanged when subjected to hydrogenation over platinum oxide in acetic acid.

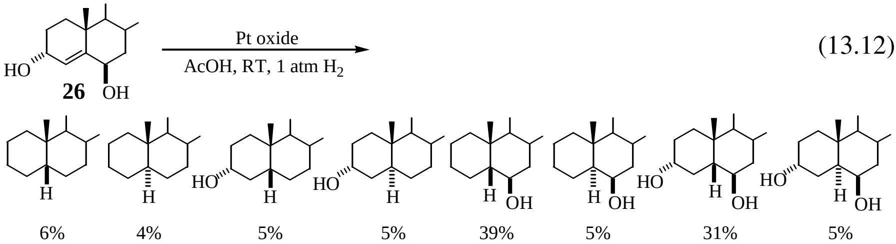
Epicholesterol β-oxide (**25**) also afforded overhydrogenolyzed products in the hydrogenation over platinum oxide in acetic acid, with uptake of 1.5 equiv of hydrogen. However, in contrast to the case with **21**, the products were largely of the 5β series (eq. 13.11).[32]



25

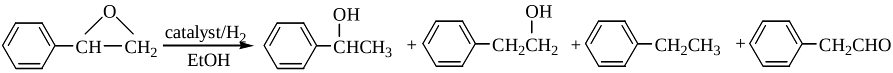
(13.11)

The results have been explained by the situation that the adsorption of **25** at the α face is strongly hindered by the axial 3α-hydroxyl group. The allylic diol **26**, which may be formed by isomerization, similarly as with **21**, has been found also to give largely the products of the 5β series (5β : 5α = 81 : 19) (eq. 13.12). A similarity in the product distribution between **25** and **26** has also been pointed out.[33] Such an effect of the 3α substituents has been known in the hydrogenation of Δ^5-steroids.[34] The extensive loss of the 6β-hydroxyl group in **22** and the 3α-hydroxyl group in **26** suggests that both the axial hydroxyl groups are liable to hydrogenolysis with ease by an S_N2-type attack of hydrogen.



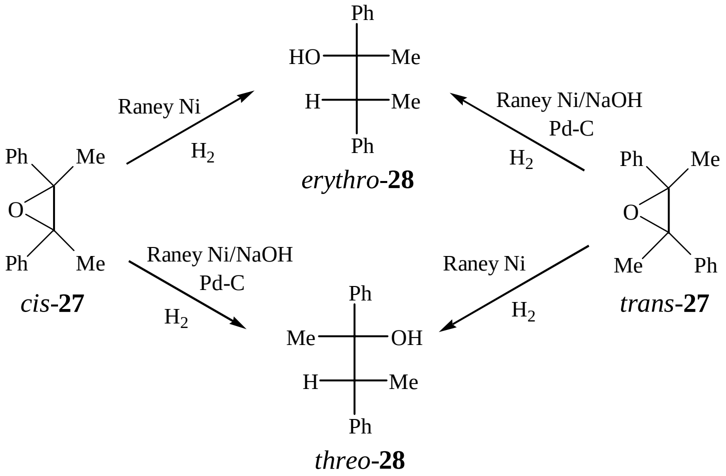
(13.12)

Hydrogenolysis of styrene oxide in ethanol affords not 1-phenylethanol but always 2-phenylethanol, together with deoxygenated products and phenylacetaldehyde (eq. 13.13). The hydrocarbon formed at the initial stages over Raney Ni was found to be



Catalyst	Additive				
Raney Ni	—	0	75	25	-
Raney Ni	NaOH	0	85	15	-
Pd–C B	—	0	100	0	+
Pd–C B	NaOH	0	100	0	+
Adams Pt	—	0	100	Trace	-

(13.13)

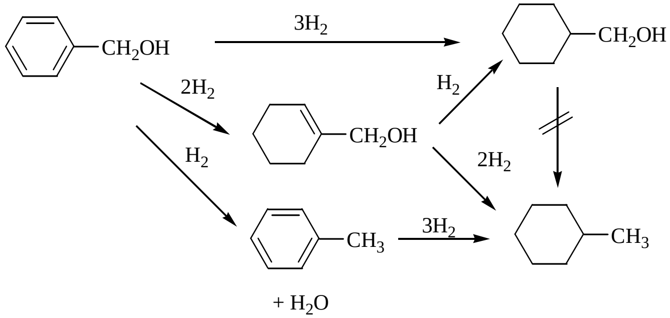


Scheme 13.4 The stereochemistry of hydrogenolysis of *cis*- and *trans*-α,α′-dimethylstilbene oxide over Pd–C and Raney Ni (ethanol, room temperature, 1 atm H_2).

styrene, which was then hydrogenated to ethylbenzene. It is noted that the formation of hydrocarbons was not observed over Pd–C B.[35] Mitsui and Nagahisa observed that the hydrogenolysis of α,α′-dimethylstilbene oxide (**27**) over Pd–C in ethanol afforded predominantly *threo*-2,3-diphenylbutan-2-ol (**28**) from *cis*-**27** and the *erythreo* isomer from *trans*-**27**, while over Raney Ni *erythro*-**28** is formed from *cis*-**27** and *threo*-**28** from *trans*-**27** (Scheme 13.4).[36] Thus, the configuration of the product **28** was inverted in the reaction over Pd–C and retained over Raney Ni. When **27** was hydrogenated with Raney Ni in the presence of a small amount of sodium hydroxide, the **28** with inverted configuration was obtained predominantly (see Scheme 13.4). It is of interest that such an effect of sodium hydroxide was not observed with Pd–C, nor in the hydrogenolysis of **28**, where the configuration of the product, 2,3-diphenylbutane, was always inverted over Pd–C and retained over Raney Ni.

13.1.3 Benzyl–Oxygen Functions

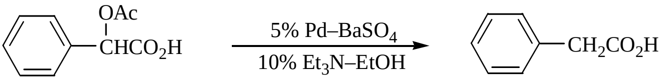
Aromatic compounds containing benzyl–oxygen functions such as benzyl alcohols, ethers, and esters are known to be extremely labile to hydrogenolysis under mild conditions. In general, the hydrogenation of the aromatic ring and the hydrogenolysis of the benzyl–oxygen linkage are competing reactions. The saturated product formed while retaining its carbon–oxygen linkage is not hydrogenolyzed under mild conditions. A part of the carbon–oxygen linkage may also be hydrogenolyzed in an allyl-type intermediate, as shown with benzyl alcohol in Scheme 13.5. Since the rate of hydrogenation of aromatic rings over catalysts such as nickel, palladium, and copper–chromium oxide is seldom as good as the rate of hydrogenolysis of benzyl–oxygen linkages, the selective hydrogenolysis of benzyl–oxygen functions to give



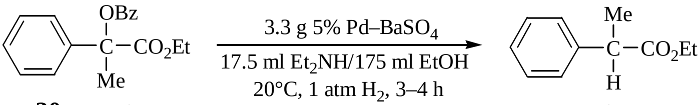
Scheme 13.5 Hydrogenation and hydrogenolysis pathways of benzyl alcohol.

aromatic hydrocarbons occurs readily over these catalysts. On the other hand, the selective hydrogenation of the aromatic rings carrying a benzyl–oxygen function without accompanying hydrogenolysis is achieved only under rather specified conditions (e.g., in the presence of a proper alkali) and/or over the special catalysts that are highly active for the hydrogenation of aromatic rings such as ruthenium and rhodium (for examples, see Section 11.3).

In general, the rate of hydrogenolysis of benzyl–oxygen bonds increases in the following order: –OH, –OR < < –OAr < $–OHR^+$ < $–OH_2^+$; –OAc < $–OCOCF_3$.[37,38] Hydrogenolysis of benzyl-type alcohols and ethers is usually promoted by acid and retarded by alkali. In some cases, however, hydrogenolysis may be promoted in the presence of an organic base. For example, hydrogenolysis of *O*-acetylmandelic acid (**29**) and ethyl *O*-benzoylatrolactate (**30**) over Pd–$BaSO_4$ can be achieved in ethanol or methanol solution containing 10% diethyl- or triethylamine as a promoter (eqs. 13.14 and 13.15).[39] These benzyl esters undergo hydrogenolysis only very slowly in neutral medium. In the case of **29** the reaction time was reduced from 300 to 10 min in the presence of triethylamine, and **30** was hydrogenolyzed only in the presence of an amine under normal conditions.



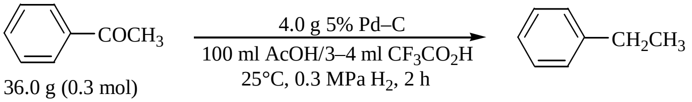
29 (13.14)



30, L-(+)-form 2.98 g (0.01 mol) D-(+)-form 1.43 g (81%) (72.9% optical purity) (13.15)

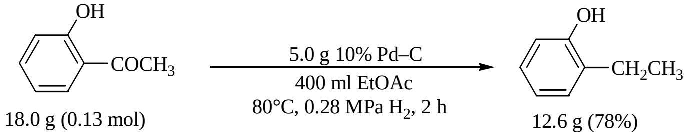
Aromatic aldehydes and ketones, ArCOR; R = H, alkyl or aryl, like the corresponding benzyl-type alcohols, are readily converted to the corresponding methylene derivatives, $ArCH_2R$, over Pd catalysts in acidic medium, particularly in the presence of

strong acid. For example, hydrogenolysis of acetophenone to ethylbenzene over Pd–C could be completed rapidly in acetic acid containing a small amount of trifluoroacetic acid (eq. 13.16).[40]

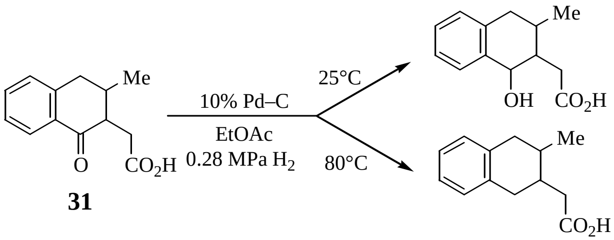


(13.16)

However, according to Hartung and Simonoff, if the aryl alkyl ketone contains a phenolic hydroxyl in the *ortho* position, hydrogenolysis to the hydrocarbon derivative does not takes place. Thus, *o*-hydroxypropiophenone and 4-acylresorcinols were not hydrogenolyzed to the corresponding alkyl derivatives over Pd–C or Raney Ni.[41] Walker, however, obtained 2-ethylphenol in 78% yield in the hydrogenation of *o*-hydroxyacetophenone over 10% Pd–C at 80°C and 0.28 MPa H_2 (eq. 13.17).[42] The oxo group of the compound **31** was hydrogenated to the hydroxyl group over 10% Pd–C in ethyl acetate at 25°C, but the hydrogenolysis to the methylene group took place at 80°C (eq. 13.18).[43]



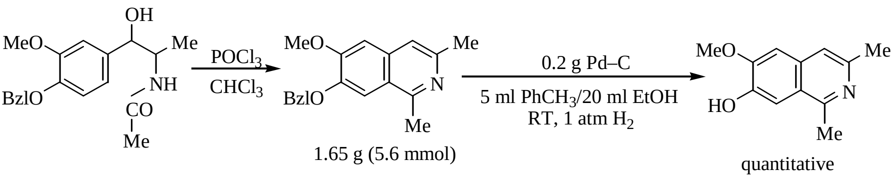
(13.17)



31

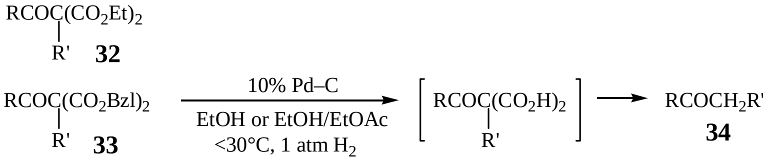
(13.18)

Catalytic debenzylation is widely utilized for removing a benzyl group introduced in order to protect a reactive function during a series of reactions. An extensive survey of the literature on this reaction is found in a review by Hartung and Simonoff.[41] Equation 13.19 illustrates a typical example of such applications.[44]



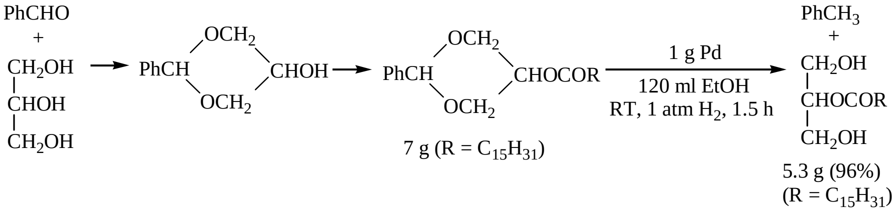
(13.19)

In an example shown in eq. 13.20, benzyl groups are employed to protect carboxyl groups. In contrast to the case with acylmalonic esters, $RCOCH(CO_2Et)_2$, conversion of fully substituted acylmalonic esters **32** into the ketones $RCOCH_2R'$ (**34**) by acidolysis was unsuccessful. However, the benzyl groups in the corresponding benzyl ester **33** can be removed selectively by hydrogenolysis over Pd–C. Decarboxylation of the resulting malonic acid afforded the required ketone **34**.[45]



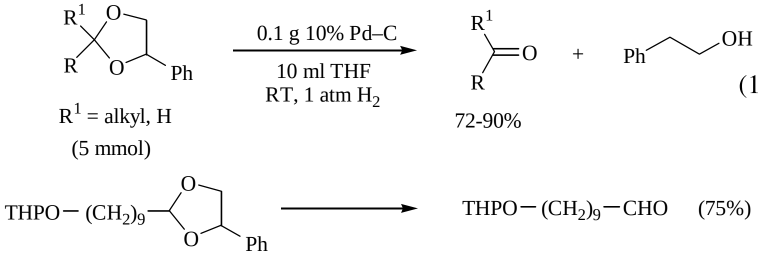
(13.20)

An acetal of benzaldehyde may become a protective group of polyhydroxy compounds. The hydroxyl groups in the 1 and 3 positions of glycerol may form a cyclic acetal with benzaldehyde. The secondary hydroxyl group left intact is available for esterification. Hydrogenolytic removal of the benzal group allows the synthesis of the β-monoglyceride (eq. 13.21).[46]



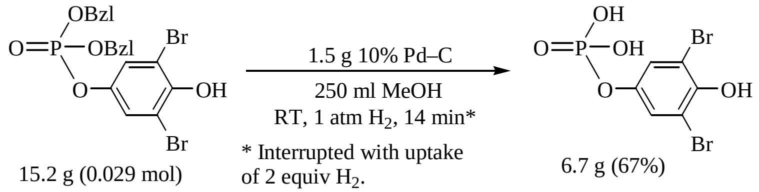
(13.21)

The deprotection of 4-phenyl-1,3-dioxolanes to liberate free carbonyl compounds over Pd–C is possible without affecting acid labile groups such as *O*-silyl ether and *O*-THP (tetrahydropyranyl) ether (eq. 13.22).[47]

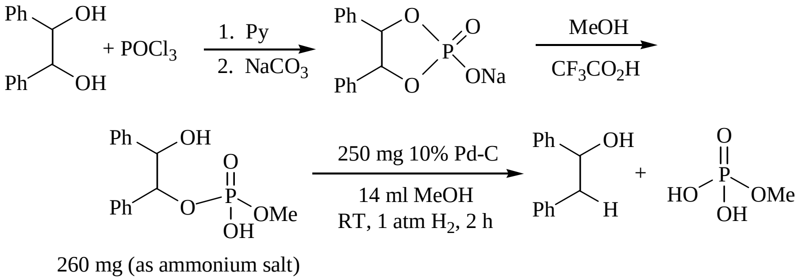


(13.22)

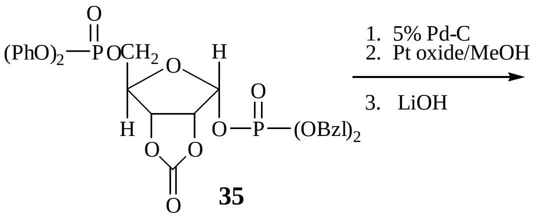
Debenzylation of the benzyl esters of phosphoric acid has been employed in the synthesis of phosphorylated alcohols. Examples are shown in eqs. 13.23[48] and 13.24.[49] Tener and Khorana synthesized α-D-ribofuranose 1,5-diphosphate (**36**) by hydrogenolysis of the benzyl phenyl phosphate **35**, first, in the presence of 5% Pd–C, and then in the presence of Adams platinum to remove, respectively, the benzyl and the phenyl groups (eq. 13.25).[50]



(13.23)

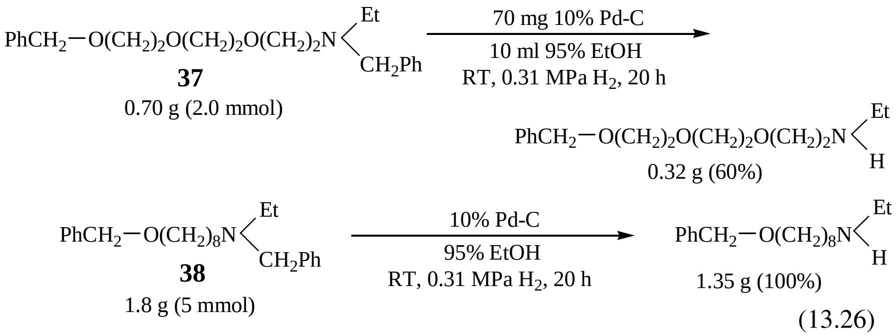


(13.24)



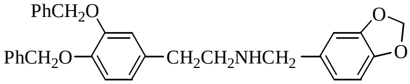
(13.25)

Hydrogenolysis of *O*-benzyl groups is generally accepted to take place more readily than that of *N*-benzyl groups.[51] However, the ease of *O*-debenzylation may be affected by the structure and, in particular, by the presence of the nitrogen bases or acids. Czech and Bartsch showed that the hydrogenolysis of benzyl nonyl ether, an alkyl benzyl ether, in 95% ethanol over Pd–C at room temperature, and 0.31 MPa H_2 was totally inhibited in the presence of 5 mol% of butylamine or *N*-benzylethylamine, but not by pyridine.[52] In contrast, the hydrogenolysis of benzyl phenyl ether, an aryl benzyl ether, proceeded smoothly in the presence of 5 or 100 mol% of butylamine.[52] These results could explain the facts that only *N*-debenzylation products were isolated from compounds **37** and **38** in yields of 60 and 100%, respectively (eq. 13.26).[52]

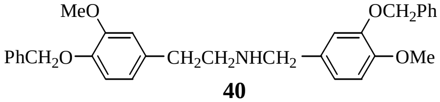


(13.26)

On the other hand, selective cleavage of *O*-benzyl groups was reported with the compounds **39**[53] and **40**[54] when hydrogenated as the hydrochloride or in the presence of hydrochloric acid.



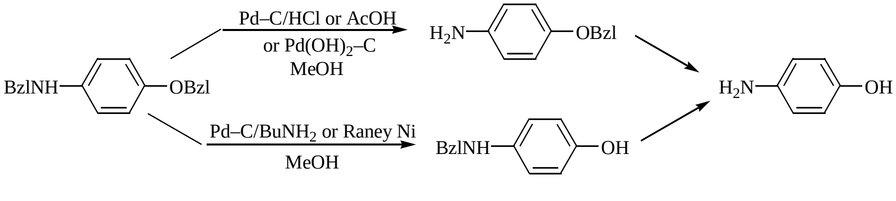
39



40

Seif et al. observed similar different effects of nitrogen bases on the *O*-debenzylation reactivity between an alkyl benzyl ether and an aryl benzyl ether.[55] Further, it was observed that the hydrogenolysis of *N*-benzylcyclohexylamine in methanol over 5% Pd–C was inhibited by adding hydrochloric acid, whereas hydrogenolysis of benzyl cyclohexyl ether was greatly promoted by hydrochloric acid.[55] Thus, it was possible to selectively hydrogenolyze an equimolar mixture of *N*-benzylcyclohexylamine and benzyl cyclohexyl ether. Only *N*-benzylcyclohexylamine was hydrogenolyzed in methanol, and only benzyl cyclohexyl ether was hydrogenolyzed when 2 equiv (for the amine) of hydrochloric acid was added.

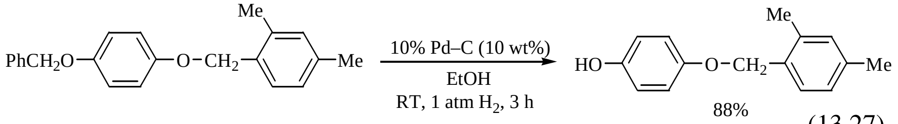
On the other hand, *N*,*O*-dibenzyl-*p*-aminophenol was selectively hydrogenolyzed to give *O*-benzyl-*p*-aminophenol with addition of hydrochloric acid or acetic acid or by changing the catalyst (10% Pd–C) to Pearlman's [10% $Pd(OH)_2$–C] in neutral methanol. Addition of 5 mol% of butylamine depressed the formation of *O*-benzyl-*p*-aminophenol and increased the selectivity for formation of *N*-benzyl-*p*-aminophenol by allowing rapid *O*-debenzylation to occur while slowing down *N*-debenzylation. Substituting Raney Ni for the palladium catalysts also resulted in faster *O*-debenzylation than *N*-debenzylation, as shown in Scheme 13.6. Sajiki et al. have found that the hydrogenolysis of benzyl protective group for phenolic hydroxyl over Pd–C is effectively depressed by the addition of ethylenediamine, diethylenetriamine, *o*-phenylenediamine, 8-aminoquinoline, 2,2′-dipyridyl, and 1,10-phenanthroline, while the addition of ammonia, methylamine, triethylamine, and pyridine is not effective.[56] Further, a Pd–C catalyst prior complexed with ethylenediamine could depress phenolic *O*-benzyl and *N*-Cbz protective groups effectively during the hydrogenation of olefinic, acetylenic, nitro, benzyl



Scheme 13.6 Selective debenzylation of *N*,*O*-dibenzyl-*p*-aminophenol.

ester, and azide groups, thus allowing the chemoselective hydrogenation of these groups in the presence of an *O*-benzyl or *N*-Cbz groups.[20] Sansanwal and Krishnamurty have found that palladium-catalyzed transfer hydrogenation using cyclohexene readily deprotects alcohol benzyl ethers and aliphatic benzyl esters, while phenol benzyl ethers and benzyl benzoates were stable under these conditions.[57] Thus, when the substrate (50 mg), 10% Pd–C (50 mg) and cyclohexene (1–2 ml) along with benzene (3–4 ml) were refluxed, the benzyl ethers of hexadecanol and cholesterol readily underwent debenzylation in 3 h, while 2-benzyloxynaphthalene, 2-benzyloxy-6-hydroxyacetophenone, benzyl 4-benzyloxybenzoate, and benzyl benzoate were essentially unchanged even in 8 h refluxing. 2′-Hydroxy-4,4′-dibenzyloxychalcone gave the corresponding dihydrochalcone but not 2′,4,4′-trihydroxydihydrochalcone.

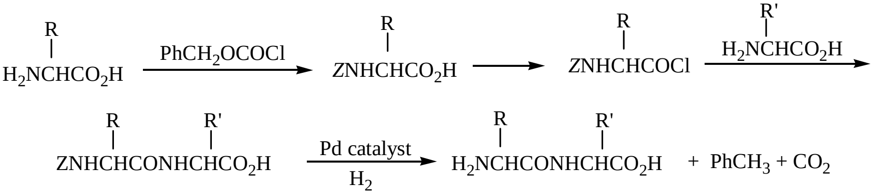
Davis and Muchowski showed that the methyl groups at the *ortho* positions of a benzyl group lead to slower hydrogenolysis, probably due to steric crowding.[58] Thus, the rates of hydrogenolysis of benzyl, 4-methylbenzyl, 2-methylbenzyl, 2,4-dimethylbenzyl, and 2,4,6-trimethylbenzyl ethers of 4-phenylphenol over 10% Pd–C in 9:1 tetrahydrofuran–ethanol decreased in the order mentioned above. The 2,4,6-trimethylbenzyl ether was not hydrogenolyzed at room temperature and 0.4 MPa H_2, but clean hydrogenolysis took place at 40–50°C. The 2,4-dimethylbenzyl ether could be completely hydrogenolyzed under 0.4 MPa H_2 at room temperature, while the benzyl ether was almost completely hydrogenolyzed at room temperature and 1 atm H_2. As expected from these findings, the selective hydrogenolysis of the mixed benzyl and 2,4-dimethylbenzyl ether of hydroquinone was successful at 1 atm H_2; 4-(2,4-dimethylbenzyloxy)phenol was isolated in 88% yield (eq. 13.27).



(13.27)

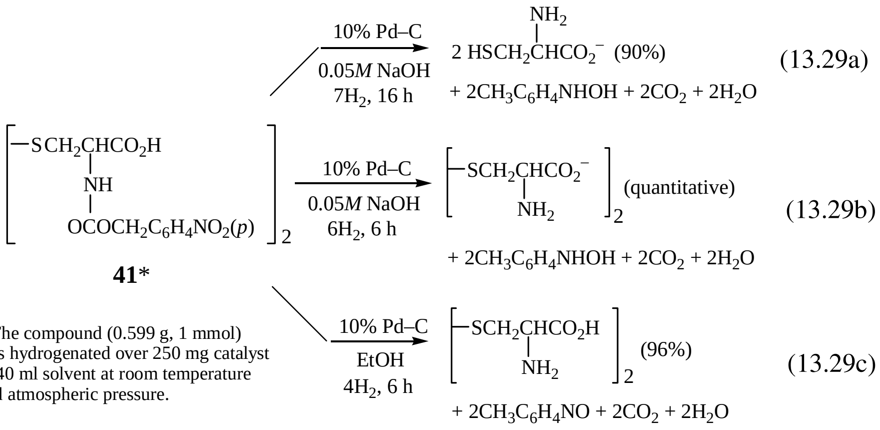
One of the most widely used applications of catalytic debenzylation is the carbobenzyloxy method for the synthesis of peptides that has been developed by Bergmann and Zervas.[59,60] In this method, a benzyloxycarbonyl group ($PhCH_2OCO$-, usually denoted Z) is introduced into an amino acid for protecting the amino group. The protected amino acid is converted into the acid chloride, which may form a peptide linkage by reaction with another molecule of amino acid. Hydrogenolysis of the protected dipeptide yields the free dipeptide, toluene, and carbon dioxide, as formulated in Scheme 13.7. Since carbon dioxide is evolved, the progress of the hydrogenolysis cannot be monitored by the amount of hydrogen absorbed and it is necessary to determine the amount of carbon dioxide evolved to evaluate the degree of the reaction. An example is given in eq. 13.28.[61]

$$\underset{\text{7.64 g (19.4 mmol)}}{ZNHCH_2CONH\overset{\overset{CO_2Et}{|}}{C}HCH_2CH_2CO_2Et} \xrightarrow[\text{100 ml EtOH/1.6 ml conc. HCl, RT, 1 atm } H_2]{\text{0.5 g Pd}} \underset{\text{5.46 g (as HCl salt) (95\%)}}{H_2NCH_2CONH\overset{\overset{CO_2Et}{|}}{C}HCH_2CH_2CO_2Et} \quad (13.28)$$



Scheme 13.7 A series of reactions involved in the peptide synthesis by the carbobenzyloxy method.

In some cases, substituted Z functions are preferred as protective groups. *p*-Bromo substituted Z was used as a protective group for more ready crystallization of the resulting amino acid derivatives and also for as high reactivity toward hydrogenolysis as the unsubstituted ones.[62] Berse et al. used successfully *p*-nitro-substituted Z group as a protective group for the synthesis of peptides containing cystine or cysteine.[63] The protective group could be removed by catalytic hydrogenolysis in the presence of the sulfur functions that were known to inhibit the catalysts, as observed by White in unsuccessful attempts to remove Z group from dicarbobenzyloxycystinyldiglycine with hydrogen and platinum or palladium black.[64] The hydrogenation of di(*p*-nitrobenzyloxycarbonyl)-L-cystine (**41**) as sodium salt in aqueous media afforded L-cysteine and *p*-tolylhydroxylamine with uptake of 7 molar equiv of hydrogen in about 16 h (eq. 13.29a). If the hydrogenation was arrested when 6 mol of hydrogen had been absorbed (about 6 h), L-cystine and *p*-tolylhydroxylamine were obtained (eq. 13.29b). When the disubstituted cystine was hydrogenated in ethanol, 4 mol of hydrogen was absorbed and cystine was obtained in 96% yield probably along with *p*-nitrosotoluene (eq. 13.29c). The method has been applied to the preparation of peptides containing cystine or cysteine. It has also been found that, if an *S*-benzyl group of cysteine is replaced by a *p*-nitrobenzyl group, it can be removed by catalytic hydrogenation (eq. 13.30), whereas *S*-benzylcysteine is cleaved only by reduction with sodium in liquid ammonia.



* The compound (0.599 g, 1 mmol) was hydrogenated over 250 mg catalyst in 40 ml solvent at room temperature and atmospheric pressure.

$$p\text{-}O_2NC_6H_4CH_2SCH_2CH(NH_2)CO_2H \xrightarrow[\substack{40\text{ ml EtOH/20 ml }1M\text{ HCl}\\ \text{RT, 1 atm }H_2\text{, 3 h}}]{0.138\text{ g 10\% Pd–C}} HSCH_2CH(NH_2)CO_2H + HOHNC_6H_4CH_3 \quad (13.30)$$

0.548 g (1.9 mmol) (as monohydrate) → 0.096 g as cystine (40%)

The Z group can be hydrogenolyzed in the presence of other protective groups such as *t*-butyl ester, *t*-butyl ether, and *N*-*t*-butoxycarbonyl (Boc) groups. *t*-Butyl esters are not affected by hydrogenation in the presence of palladium or platinum and are much more readily removed by acid catalysis (eq. 13.31).[65]

$$\underset{8.2\text{ g}}{\text{Z·Gly–Phe·O-}t\text{-Bu}} \xrightarrow[\substack{100\text{ ml EtOH}\\ \text{RT, 1 atm }H_2\text{, 1 h}}]{2\text{ g 10\% Pd–C}} \underset{3.8\text{ g (66\%)}}{\text{H·Gly–Phe·O-}t\text{-Bu}} \quad (13.31)$$

In the example shown in eq. 13.32, the Z group on the compound **42** could be selectively removed when carefully hydrogenated. When the reaction was performed in the presence of acetic anhydride, the *N*-acetylated product **43** was obtained in 65% yield. Prolonged hydrogenation further removed the remaining benzyl group to give the diacetate **44**.[66]

$$\underset{\mathbf{42}}{\text{Boc–NH(CH}_2)_3\text{–N(OBzl)–Z}} \xrightarrow[\substack{\text{EtOAc (0.1}M\text{ solution)}\\ Ac_2O\text{ (2.5 equiv)}\\ 0^\circ\text{C, 1 atm }H_2\text{, 3 h}}]{5\%\text{ Pd–C (15–20 wt \%)}} \underset{\mathbf{43}\ \ 65\%}{\text{Boc–NH(CH}_2)_3\text{–N(OBzl)–Ac}} \longrightarrow \underset{\mathbf{44}}{\text{Boc-NH(CH}_2)_3\text{-N(OAc)-Ac}} \quad (13.32)$$

Catalytic debenzylation has also been applied successfully to the solid-phase peptide synthesis developed by Merrifield.[67] Schlatter et al. have shown that catalytic hydrogenolysis of benzyl-ester-bound peptide resins can be accomplished by swelling the peptide resins in either *N*,*N*-dimethyformamide or tetrahydrofuran solutions of palladium(II) acetate and subjecting them to molecular hydrogen. Hydrogenolyses were effectively performed at 40°C and 0.41 MPa H_2. Some commonly used blocking groups such as Boc, acetyl, trifluoroacetyl, and tosyl were stable to the catalytic hydrogenolysis.[68,69] The mild conditions also minimize the concern of racemization, which could be a problem in the methods of peptide resin cleavage utilizing basic reagents.[70] A typical example is outlined in eq. 13.33.[69]

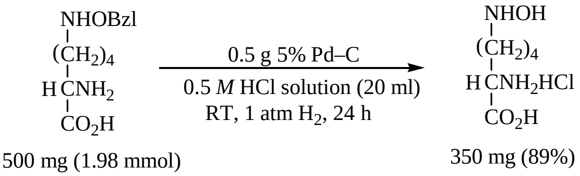
$$\underset{5.50\text{ g (0.0035 mol)}}{\text{Boc–Tyr–Gly–Gly–Phe–Val–OCH}_2C_6H_4\text{–resin}} \xrightarrow[\substack{55\text{ ml DMF}\\ 39^\circ\text{C, 0.41 MPa }H_2\text{, 24 h}}]{Pd(OAc)_2\text{ (2.37 g, 0.0106 mol)}} \quad (13.33)$$

$$\text{Solids recovered} \xrightarrow[\substack{55\text{ ml DMF}\\ 39^\circ\text{C, 0.41 MPa }H_2\text{, 24 h}}]{Pd(OAc)_2\text{ (0.79 g, 0.0035 mol)}} \underset{1.60\text{ g (71\%)}}{\text{Boc–Tyr–Gly–Gly–Phe–Val–OH}}$$

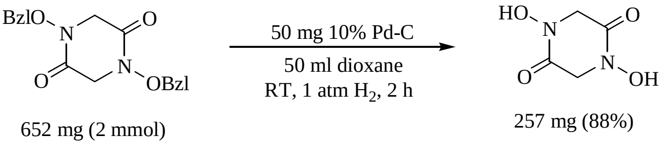
The utility of this method was demonstrated in the synthesis of a biologically active pentapeptide leucin enkephalin (**45**) where Boc-protected **45** (**46**) could be removed from the resin in 88% yield (56% after purification).[70]

H–Tyr–Gly–Gly–Phe–Leu–OH **45** Boc–Tyr–Gly–Gly–Phe–Leu–OH **46**

Palladium-catalyzed debenzylation has also been shown to be effective to remove the benzyl group from *N*-benzyloxy amino acids or their peptides.[66,71–74] Examples are shown in eqs. 13.34[71] and 13.35.[73] When the hydrogenolysis in eq. 13.34 was carried out in a neutral solution, that is, in aqueous methanol, L-lysine was obtained in 51% yield.



(13.34)



(13.35)

Shimizu et al. studied the debenzylation of *N*-benzyloxy peptide **47**.[74] The most satisfactory results were obtained by hydrogenolysis over Pd–C in methanol (eq. 13.36), rather than by use of HBr/AcOH or $(CF_3CO_2)_3B/CF_3CO_2H$.[74]

Pht=Gly–DL-(BzlO)Phe–Gly–OMe **47** 2.65 g (5 mmol) —[0.03 g 10% Pd-C / 10 ml MeOH / 30°C, 1 atm H_2, 24 h]→ Pht=Gly–DL-(HO)Phe–Gly–OMe 1.93 g (88%)

(13.36)

Transfer hydrogenation over Pd–C or palladium black with cyclohexene as a hydrogen donor has been found to be effective for the removal of *N*-Z and benzyl ester groups, as shown by Jackson and Johnstone[75] and Anantharamaiah and Sivanandaiah.[76] According to the procedure by Anantharamaiah and Sivanandaiah, the protected peptide is dissolved in a mixture of ethanol and cyclohexene (acetic acid may be added to assist dissolution) and the solution is refluxed with stirring in the presence of Pd–C or palladium black. The quantity of catalyst required is quite large, but the catalyst can be reused. If freshly prepared palladium black is used, other protecting groups such as N^{im}-benzyl (histidine), benzyl ether (tyrosine, serine), and nitro (arginine) can also be removed much more rapidly than in the usual catalytic hydrogenations. The method is also useful for the removal of *N*-Z group from peptides having sulfur-containing amino acids. The Boc group is unaffected under these conditions. Equation 13.37 illustrates an example for removing Z group by this hydrogen transfer method.

Z–Ser–Gly–OBzl —(90 mg 10% Pd-C / 4 ml cyclohexene/8 ml EtOH / refluxed for 1.5 h)→ H–Ser–Gly–OH (13.37)
180 mg (0.466 mmol) 100 mg (90%)

Felix et al. found that 1,4-cyclohexadiene was a very effective hydrogen donor for catalytic transfer hydrogenation.[77] *N*-Z, benzyl ester, and tyrosine benzyl ether protecting groups were rapidly removed at 25°C in the presence of 10% Pd–C. Transfer hydrogenation of *N*-Z-L-alanine in ethanol at 25°C with 1,4-cyclohexdiene and 10% Pd–C required only 1.5 h for complete deprotection, while there was no deprotection with cyclohexene even after 24 h at 25°C. A more efficient palladium black was required for removal of N^{im}-benzyl group from histidine, the N^{g}-nitro group from arginine, and the benzyl ether groups from serine and threonine at 25°C. *t*-Butyl-derived protecting groups were completely stable under these conditions. Glacial acetic acid was found to be the most effective solvent. Other solvents such as ethanol, dimethylacetamide, methanol, and dimethylformamide were also useful, although they required somewhat longer reaction times. An example is shown in eq. 13.38. The *N*-Z group was removed from methionine by the transfer hydrogenation in ethanol using palladium black, but not from *S*-benzylcysteine, even in the presence of glacial acetic acid at elevated temperatures.

Boc–Phe–Gln–OBzl —(10% Pd–C (an equal weight per protecting group) / 4 ml absolute EtOH / 0.94 ml 1,4-cyclohexadiene (10.0 mmol) / 25°C)→ Boc–Phe–Gln–OH (13.38)
1.0 mmol 84%

The catalytic transfer hydrogenolysis has been applied successfully by Colombo to cleave benzyl ester–type linkage to the Sparrow modified polystyrene support in the solid-phase peptide synthesis.[78] 1,4-Cyclohexadiene was found to be the most effective hydrogen donor, together with in situ–generated palladium black. Hydrogenations were carried out at 30–40°C in dimethylformamide or glacial acetic acid to remove protected amino acids and peptides in 81–92% yields after 3–4 times in all reactions except in the case of *S*-containing Boc–Met–Oresin where Boc-Met-OH was obtained in lower yield (67%). Sivanandaiah and Gurusiddappa[79] and ElAmin et al.[80] used formic acid as an effective hydrogen donor for rapid removal of benzyl and Z protecting groups by catalytic transfer hydrogenation. Usually, hydrogenolysis takes place rapidly at room temperature. Unlike cyclohexene or cyclohexadiene, formic acid is an excellent solvent for most peptides and peptide derivatives. Lower concentrations of formic acid in methanol also result in rapid removal of benzyl and Z groups but reduce the possibility of removal of acid-labile protecting groups. Thus, in methanol containing 4.4% of formic acid, the Boc group is stable and Boc–AspOH was obtained in 98% yield from Boc–Asp(*O*-Bzl). The Boc group can be removed with 98–100% formic acid. The transfer hydrogenation using formic acid is also effective for the removal of not only the nitro group from nitroarginyl peptides but also the protecting groups from methionine-containing peptides. Examples are given in eqs. 13.39,[80] 13.40[80] and 13.41.[79]

$$\underset{\sim 200\ \text{mg}}{\text{Z–Phe–Phe–OEt}} \xrightarrow[\substack{12\text{–}22\ \text{ml 4.4\% HCO}_2\text{H-MeOH} \\ \text{RT, 10 min}}]{200\ \text{mg Pd black}} \underset{97\%}{\text{HPhe–Phe–OEt}\cdot\text{formate}} \qquad (13.39)$$

$$\underset{\sim 200\ \text{mg}}{\text{Z–Lys}(N^{\varepsilon}\text{-Bzl})} \xrightarrow[\substack{12\text{–}22\ \text{ml 4.4\% HCO}_2\text{H-MeOH} \\ \text{RT, 10 h}}]{200\ \text{mg Pd black}} \underset{81\%}{\text{HLys}\cdot\text{formate}} \qquad (13.40)$$

$$\underset{100\ \text{mg}}{\text{Boc–Trp–Ser(Bzl)–Tyr–OMe}} \xrightarrow[\substack{1.2\ \text{ml 98–100\% HCO}_2\text{H} \\ \text{RT, 3 h}}]{90\ \text{mg Pd black}} \underset{81\%}{\text{HTrp–Ser–Tyr–OMe}\cdot\text{formate}} \qquad (13.41)$$

Coleman and Royer employed Pd-poly(ethyleneimine) "ghost" as an effective catalyst for the hydrogen transfer hydrogenolysis of Z group in peptide synthesis, using formic acid as a hydrogen donor.[81]

Removal of the Z group from *S*-containing amino acids and peptides often encounters difficulty. Yajima et al. have shown that the poisoning effect of the S group in methionine and the peptides containing methionine may be suppressed by adding BF_3–etherate, as seen in an example in eq. 13.42.[82]

$$\underset{1.41\ \text{g (5 mmol)}}{\text{MeSCH}_2\text{CH}_2\overset{\text{NHZ}}{\overset{|}{\text{C}}}\text{HCO}_2\text{H}} \xrightarrow[\substack{50\ \text{ml MeOH} \\ 3.1\ \text{ml BF}_3\ \text{etherate (5 equiv)} \\ 40^\circ\text{C, 1 atm H}_2,\text{* 7 h}}]{0.5\ \text{g Pd–C (Zelinsky)}} \begin{array}{l} \text{MeSCH}_2\text{CH}_2\overset{\text{NH}_2}{\overset{|}{\text{C}}}\text{HCO}_2\text{H (53\%)} \\ \text{MeSCH}_2\text{CH}_2\overset{\text{NH}_2}{\overset{|}{\text{C}}}\text{HCO}_2\text{Me (31\%)} \end{array}$$

* Bubbled into the solution.

(13.42)

Losse et al. have demonstrated that the difficulty in the hydrogenolytic debenzylation of *S*-protected cysteine derivatives is due to the strong poisoning action of thiols that may be formed probably by a β elimination of the cysteine to give the dehydroalanine derivative.[83] The overall reaction in the case of Z–Cys(Bzl)–OBzl may be formulated as in eq. 13.43.

$$\text{Z–Cys(Bzl)–OBzl} + 3\text{H}_2 \xrightarrow{\text{Pd}} \text{PhCH}_2\text{SH} + {}^{-}\text{OOCAlaOH} + 2\text{PhCH}_3 \qquad (13.43)$$

The extent of suppression, however, depended on the position of the cysteine and on the sequence length of the peptide derivative, as seen from the results in Table 13.4. Thus, the efficiency of BF_3 is not satisfactory in simple cysteine derivatives or peptides with a terminal protected cysteine.

13.1.4 Stereochemistry of the Hydrogenolysis of Benzyl–Oxygen Compounds

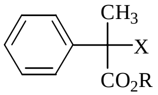
Bonner et al. found that the hydrogenolysis of optically active methyl or ethyl atrolactates (**48**, X = OH) in refluxing ethanol with large amounts of Raney Ni proceeded largely with retention of configuration; methyl D-(+)-2-phenyl-2-methoxypropionate

TABLE 13.4 Hydrogenolysis of N^{α}-Z-*S*-Ethylcysteine Derivatives with Addition of BF_3-etherate[a]

Substrate	Yield of N^{α}-Deblocked Product (%)
Z-Gly-Cys(*S*-Et)-Gly-OMe[b]	28
Z-Ala-Ala-Cys(S-Et)-OMe[b]	33
Z-Cys(*S*-Et)-Ala-Ala-OMe[b]	5
Z-Cys(*S*-Et)-OH[c]	0
Z-Gly-Cys(*S*-Et)-Gly-OMe[c]	30
Z-Ala-Ala-Cys(*S*-Et)-OMe[c]	37
Z-Ala-Ala-Cys(*S*-Et)-Ala-Ala-OMe[c]	95

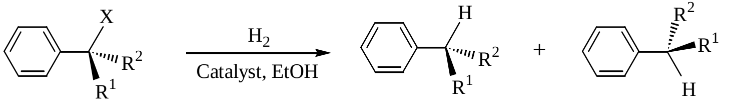
[a]Data of Losse, G.; Stiehl, H.-U.; Schwenzer, B. *Int. J. Peptide Protein Res.* **1982**, *19*, 114. Reprinted with permission from Munksgaard International Publishers Ltd.
[b]The substrate (11.48 μmol) was hydrogenated over 100 mg Pd black in 4 ml DMF with addition of 100 equiv of BF_3–etherate at 20°C and 1 atm H_2 for 1 h.
[c]The substrate (12 μmol) was hydrogenated over 25 mg Pd black in 4 ml DMF/benzene (1:3) with addition of 100 equiv of BF_3–etherate at 30°C and 1 atm H_2 for 3 h.

(**48**, X = OMe) was also hydrogenolyzed with predominant retention of configuration.[84,85] Later extensive studies by Mitsui, Imaizumi, and co-workers have revealed that the stereochemistry of hydrogenolysis of benzyl–oxygen linkages depends on the structure of compounds and the nature of catalysts as well as additives, as seen from the results summarized in Table 13.5.[86–88] When X = OH, OMe and OEt in **48**, the products with retention of configuration were obtained in 84–90% optical purities, while the products with inversed configuration predominated when X = OAr (Ar: Ph, *o*- and *p*-tolyl, and 2-naphthyl). In contrast to the results with Raney Ni, over palladium catalysts 2-phenyl-2-butanol, 2-phenyl-2-methoxybutane, ethyl atrolactate, and 2-phenyl-2-methoxypropionate were always hydrogenolyzed with inversion of configuration. The hydrogenolysis of 2-phenyl-2-butanol and its methyl ether over reduced nickel gave predominantly the inverted products in contrast to the results with Raney Ni. However, in the presence of sodium hydroxide, 2-phenyl-2-butanol gave the product with retention of configuration over reduced nickel, while the stereochemistry was not changed by alkali with its methyl ether. The acetyl and benzoyl derivatives of 2-phenyl-2-butanol and atrolactate were hydrogenolyzed with inversion over both nickel and palladium catalysts, except in the case of the benzoyl derivative of ethyl atrolactate with palladium metal, where the product with retention of configuration was formed in excess.



48
(R = Me or Et)

TABLE 13.5 Stereochemistry of the Hydrogenolysis of Benzyl–Oxygen Compounds over Nickel and Palladium Catalysts[a]



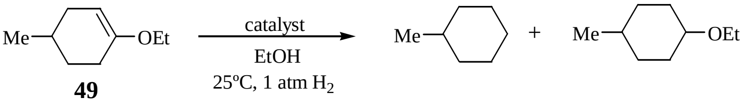
Compound							Configuration of Product	
R^1	R^2	X	Catalyst	Additive	T (°C)	H_2 P (MPa)	Retention (%)	Inversion (%)
Me	Et	OH	Raney Ni	—	10	0.1	95.5	4.5
			Ni	—	120	10	14.5	85.5
			Ni	NaOH	160	10	98	2
			Pd	—	10	0.1	5.5	94.5
Me	Et	OMe	Raney Ni	—	60	0.1	94	6
			Raney Ni	NaOH	60	0.1	28.5	71.5
			Ni	—	120	10	33.5	66.5
			Pd	—	20	0.1	4.5	95.5
Me	Et	OAc	Raney Ni	—	20	0.1	8	92
			Ni	—	50	10	2	98
			Pd	—	20	0.1	8	92
Me	CO_2Et	OH	Raney Ni	—	20	0.1	99	1
			Ni	—	110	10	85.5	14.5
			Pd	—	20	0.1	2.5	97.5
Me	CO_2Et	OMe	Raney Ni	—	20	0.1	95	5
			Raney Ni	NaOH	20	0.1	27	73
			Pd	—	10	0.1	2.5	97.5

Me	CO_2Et	OPh	Raney Ni	—	RT	0.1	15	85
			5% Pd–C A	—	RT	0.1	66.5	33.5
			5% Pd–C A	NaOH	RT	0.1	7.5	92.5
			5% Pd–C B	—	RT	0.1	15.5	84.5
			5% Pd–C B	HCl	RT	0.1	65.5	34.5
Me	CO_2Et	OAc	Raney Ni	—	20	0.1	16.5	83.5
			Raney Ni	NaOH	20	0.1	9	91
			Ni	—	140	10	5	95
			Pd	—	20	0.1	5	95
			5% Pd–C	—	20	0.1	6	94
Me	CO_2Et	OBz	Raney Ni	—	20	0.1	31.5	68.5
			Raney Ni	NaOH	20	0.1	15	85
			Pd	—	20	0.1	67	33
			5% Pd–C	—	20	0.1	38.5	61.5
			Raney Pd	—	20	0.1	12.5	87.5

[a]Data of Mitsui, S.; Imaizumi, S.; Esashi, Y. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 2143; Mitsui, S.; Imaizumi, S. *Kogyo Kagaku Zasshi* **1965**, *68*, 816. Reprinted with permission from Chemical Society of Japan.

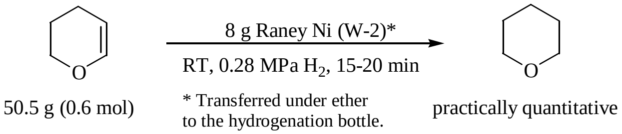
13.1.5 Vinyl–Oxygen Compounds

Vinyl ethers (enol ethers) and vinyl esters are labile to hydrogenolysis, the extents of which largely depend on the nature of catalyst and reaction conditions, as well as on their structures. The proportion of hydrogenolysis at the initial stage of the hydrogenation (given in parentheses) of 1-ethoxy-4-methyl-1-cyclohexene (**49**) (eq. 13.44) over the platinum group metals in ethanol at 25°C and 1 atm H_2 increased in the following order: Pd (1.1) < Ru (1.9) < < Os (8.2) < Rh (10.0) < Ir (14.8) < < Pt (71.6).[9] It is noted that, in contrast to the benzyl–oxygen compounds, palladium shows the least tendency toward hydrogenolysis for the vinyl ether, while platinum causes hydrogenolysis far more extensively than any of the other metals. Ruthenium is among the catalysts with the least tendency for hydrogenolysis for both benzyl- and vinyl-oxygen compounds. The extent of hydrogenolysis over rhodium is greatly affected by the nature of solvent. The amount of hydrogenolysis with **49** varied from 8.5% in ethanol to 1.1% in *t*-butyl alcohol and 0.34% in isopropyl ether.



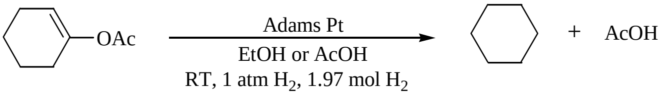
49 (13.44)

Over Raney Ni, enol ethers appear to be saturated with little hydrogenolysis. Dihydropyran is hydrogenated almost quantitatively to tetrahydropyran over Raney Ni at room temperature and 0.28 MPa H_2 (eq. 13.45).[89] Over platinum, however, 1-pentanol is formed along with tetrahydropyran.[90]

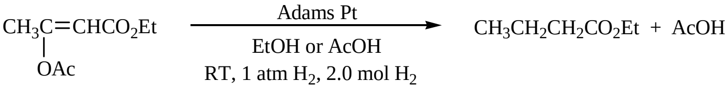


(13.45)

Enol esters are much more labile to hydrogenolysis than enol ethers. Thus, 1-acetoxycyclohexene and ethyl 3-acetoxycrotonate are almost quantitatively hydrogenolyzed over Adams platinum in ethanol or acetic acid (eqs. 13.46 and 13.47).[91,92]



(13.46)

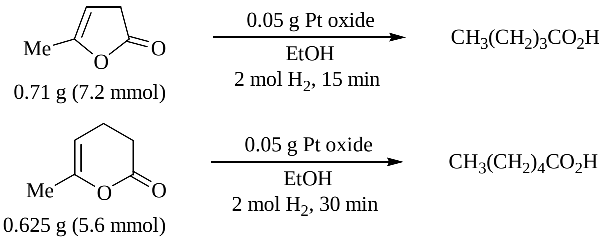


(13.47)

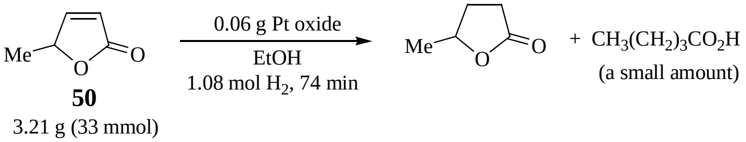
Over Pd–$CaCO_3$, however, 1-acetoxycyclohexene was hydrogenated with little hydrogenolysis to give cyclohexyl acetate in good yield.[91] In contrast to the cyclo-

hexenyl derivative, 1-acetoxycyclopentene was hydrogenated to give cyclopentyl acetate over both platinum oxide and Pd–$CaCO_3$. Similarly, 17-oxo steroid enol acetates were hydrogenated without hydrogenolysis to yield the corresponding 17β-acetoxy derivatives over both platinum oxide and Pd–$CaCO_3$.[91]

Jacobs and Scott studied the hydrogenation of various unsaturated γ- and δ-lactones over Adams platinum in ethanol.[93] Similar to enol esters, these enol lactones are readily hydrogenolyzed over platinum, as seen in the examples shown in eq. 13.48. In contrast, hydrogenolysis takes place only slightly with an α,β-unsaturated γ-lactone **50** (eq. 13.49). The saturated lactones were not reduced at all under the reaction conditions.

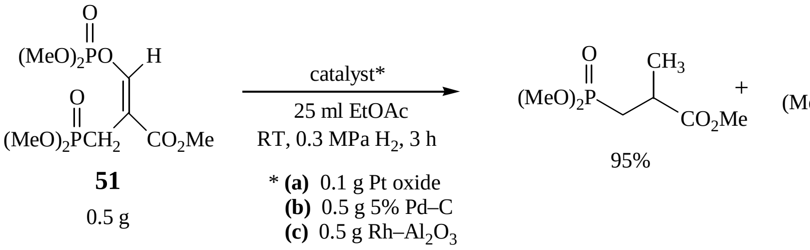


(13.48)

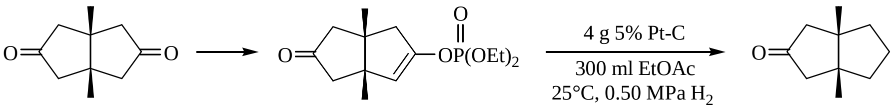


(13.49)

The phosphoric acid ester of an enol ether is even more readily hydrogenolyzed than an enol acylate. When the (*Z*)-enol phosphate **51** was subjected to hydrogenation in ethyl acetate at 0.3 MPa H_2, the hydrogenolysis products were isolated in 95% yield not only over platinum oxide but also over 5% Pd–C and 5% Rh–Al_2O_3 (eq. 13.50).[94] The hydrogenolysis of an enol phosphate has been utilized in conversion of one of two oxo groups to the methylene as shown in eq. 13.51.[95]



(13.50)

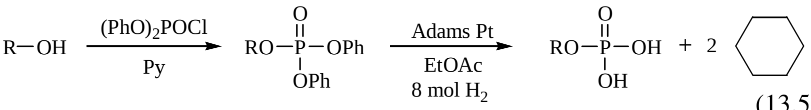


61 g (0.20 mol)

(13.51)

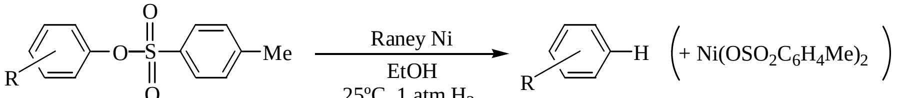
Aryl ethers and esters, like enol ethers and esters, may undergo extensive hydrogenolysis. Generally, the extents of hydrogenolysis are greater over the third-row group VIII metals (Os, Ir, Pt) than over the second-row metals (Ru, Rh, Pd).[96] The weak tendency of palladium toward the hydrogenolysis of aryl ethers may be due to the circumstances that over palladium the aryl ethers are hydrogenated largely via the corresponding enol ethers as intermediates that are hydrogenated with only slight hydrogenolysis over this metal.[96]

Phenol derivatives bonded to a strong electron-withdrawing group are readily hydrogenolyzed and may find synthetic applications. Thus, phenyl phosphates are easily hydrogenolyzed, particularly over platinum, which may be applied for removing the phenyl groups in the synthesis of glucose phosphates,[97] as in an example in eq. 13.52[98] (see also eq. 13.25).

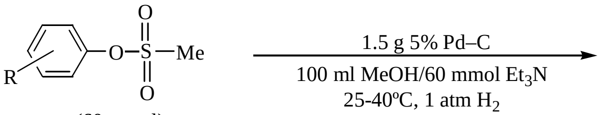


(R = 1,2,3,6-tetraacetyl-β-D-glucose residue) (13.52)

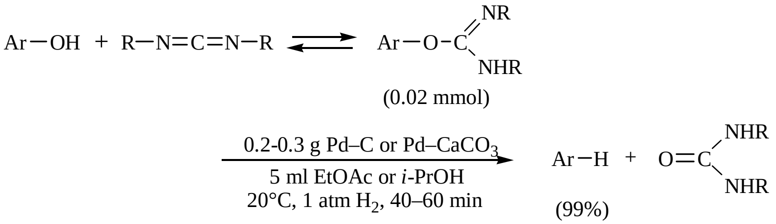
The phenyl groups in the examples given in eqs. 13.53–13.55[99–101] are hydrogenolyzed without saturation over Raney Ni or palladium. The hydrogenolysis may be utilized for removing a phenolic hydroxyl group. In aryl sulfonates, the catalyst must be employed in a large excess amount with Raney Ni (eq. 13.53), while use of a catalytic amount is sufficient with palladium (eq. 13.54).



(13.53)



(60 mmol) (13.54)

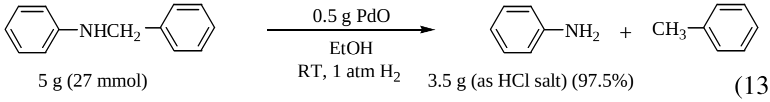


(13.55)

(Ar = 4-biphenylyl; R = cyclohexyl)

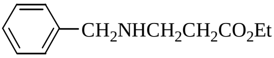
13.2 HYDROGENOLYSIS OF CARBON–NITROGEN BONDS

Carbon–nitrogen bonds are usually less readily hydrogenolyzed than carbon–oxygen bonds. Thus, benzylamine, *N*-alkylbenzylamine, and dibenzylamine are stable over palladium catalysts under mild condition.[41,102] *N*-Arylbenzylamines, however, undergo hydrogenolysis much more readily than do the *N*-alkyl derivatives. For example, *N*-benzylaniline is hydrogenolyzed quantitatively to give aniline over palladium oxide in ethanol at room temperature and atmospheric hydrogen pressure (eq. 13.56).[102]

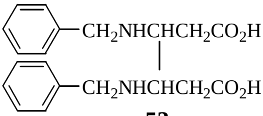


(13.56)

Dibenzylamine appears to be stable over palladium under mild conditions, since tribenzylamine is hydrogenolyzed to give dibenzylamine in almost quantitative yield in hydrogenation over palladium oxide in acetic acid or as hydrochloride in water. Certain secondary *N*-alkylbenzylamines with a substituted *N*-alkyl group such as compounds **52**,[103] **53**,[104] **54**,[105] and **55**[106] may undergo hydrogenolysis to yield the corresponding primary amines. The compound **52** was debenzylated in ethanol over a palladium–platinum catalyst supported on carbon (Pd from 0.3 g palladium chloride and Pt from 0.15 g of platinum chloride) at 1.3 MPa H_2. In the case of **53**, debenzylation was performed over 2.5% Pd–C in acetic acid containing a large excess of hydrochloric acid at 35–60°C and 0.5 MPa H_2. Compound **54** was subjected to debenzylation with palladium catalyst in the presence of an equivalent quantity of oxalic acid. Compound **55** was debenzylated as hydrochloride over 20% Pd–C in methanol at 25°C and 0.1 MPa H_2. Dahn et al. found that the ease of hydrogenolysis of benzyl-type carbon–nitrogen bonds over 10% Pd–C in ethanol at room temperature and atmospheric pressure increased in the following order: benzyl < *p*-phenylbenzyl < benzhydryl < fluorenyl < α- and β-menaphthyl (naphthylmethyl).[107] Baltzly and Russell have shown that the order of *para* substituents in stabilizing the C–N bond is given by that shown in Scheme 13.8, based on the results of competitive debenzylation of a series of 4,4′-disubstituted *N*-methyldibenzylamines, usually as the hydrochlorides over Pd–C in methanol.[108] All these substituents were stabilizers, as compared to hydrogen. *N*,*N*-Dialkybenzylamines undergo hydrogenolysis rather readily, and this reaction provides an excellent preparative method for pure dialkylamines (eq. 13.57)[109] and mixed dialkylamines (eq. 13.58).[110]



52



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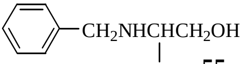
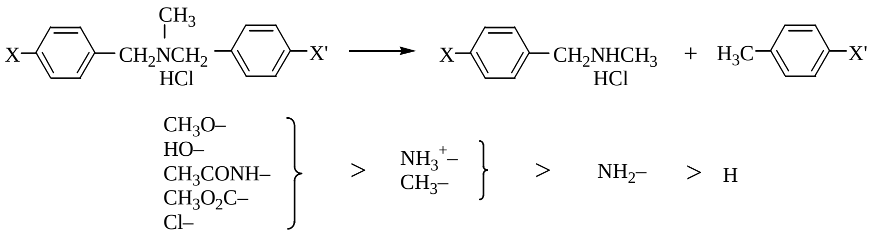


55

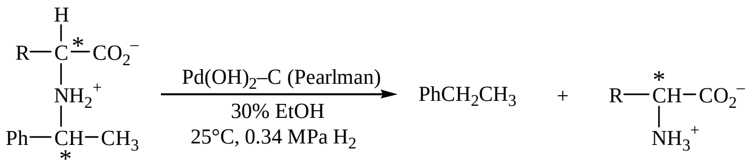


Scheme 13.8 The effect of the *para* substituents on the hydrogenolysis of *N*-methyl-dibenzylamine hydrochlorides.

$$\underset{}{PhCH_2NH_2} \xrightarrow{2C_6H_{13}Br} \underset{27\text{ g }(0.098\text{ mol})}{PhCH_2N(C_6H_{13})_2} \xrightarrow[\substack{30\text{ ml AcOH} \\ 70^\circ\text{C, 1 atm }H_2\text{, 6 h}}]{0.4\text{ g Pt oxide}} \underset{\text{almost quantitative}}{HN(C_6H_{13})_2} \quad (13.57)$$

$$PhCHO \xrightarrow{H_2NR} PhCH{=}NR \xrightarrow[\substack{AcOH \\ RT}]{\text{Pt oxide}/H_2} PhCH_2NHR \xrightarrow{R'X} PhCH_2NRR' \xrightarrow[\substack{AcOH \\ 65\text{–}75^\circ\text{C, 0.3 MPa }H_2}]{\text{Pt oxide }(\sim 1\%)} HNRR' \quad (13.58)$$

With certain *N*-benzyl compounds, it was recognized that debenzylation could be performed more successfully by use of Pearlman's $Pd(OH)_2$–C[111] as catalyst than by the usual Pd–C catalysts.[112–114] Hiskey and Northrop utilized optically active benzylamines for the preparation of optically active α-amino acids by reaction with α-oxo acids followed by hydrogenation and debenzylation.[112] The reactions involved have been described in Section 6.6 and Scheme 6.11. The debenzylation in the final step (Scheme 13.9) was unsuccessful with 10% Pd–C (Mozingo),[115] platinum oxide, or Raney Ni. However, by use of the Pearlman catalyst, α-amino acids (12.6–81.5% optical purity) were obtained in 0–85% yields.[112] Harada obtained optically active α-amino acids in 40–60% ee, using (*S*)-/(*R*)-α-phenylglycine as an optically active benzylamine component, in hydrogenolysis over Pd–C in an alkaline aqueous solution.[116] The effects of the structure of alkyl phenylglucinates and those of the solvents on the transamination reaction have also been studied (see Section 6.6).[117,118] The failure of Pd–C and a successful use of Pearlman's $Pd(OH)_2$–C in debenzylation of *N*-benzyl compounds, as observed in the reaction given in Scheme 13.9, have prompted the author to study the factors affecting the catalytic activities of palladium catalysts in the hydrogenolysis of *N*,*N*-diethylbenzylamine as a model compound.[119] From the results summarized in Table 13.6, it is seen that Pd-C (N. E. Chemcat) and Pd-C (Mozingo) were significantly deactivated when contacted with methanol (catalysts 14, 21, 26) or ethanol (catalysts 16, 23, 28), while $Pd(OH)_2$–C (Pearlman) was practically not affected



Scheme 13.9 Hydrogenolytic removal of α-phenylethyl group over palladium catalyst in asymmetric transfer amination of α-oxo acids.

with the alcohols. Deactivation of the Pd–C catalysts with the alcoholic solvents can be avoided by pretreating the catalysts with hydrogen in cyclohexane (catalysts 13, 15, 20, 22, 25, 27). On the other hand, the activity of Pearlman's catalyst became considerably lower when the solvent for prereduction was replaced by a new portion (compare catalysts 1 and 2; catalysts 3 and 4; catalysts 5 and 6; catalysts 7 and 8). Such a phenomenon was not observed with well-washed $Pd(OH)_2$–C (Pearlman). Since small amounts of acetic acid have been found to promote the hydrogenolysis (compare catalysts 9 and 11; catalysts 13 and 17), it is probable that Pearlman's catalyst was promoted by the acetic acid used for washing the catalyst and remaining in the catalyst. The hydrogenolysis is depressed by the addition of HCl (catalysts 12, 19) or NaOH (catalyst 24). The rate increase with addition of only a small amount of HCl to Pd–C (N. E. Chemcat) (catalyst 18) is probably caused by neutralization of alkaline substances contained in the catalyst with HCl, since well-washed Pd–C (N. E. Chemcat) exhibited a higher activity than the unwashed one (compare catalysts 20 and 22 with catalysts 13 and 15, respectively). Thus, it is seen that Pd–C (N. E. Chemcat) catalyzes the hydrogenolysis of *N*,*N*-diethylbenzylamine as effectively as or even more effectively than Pearlman's catalyst, by avoiding direct contact with methanol or ethanol by pretreating the catalyst with hydrogen in cyclohexane followed by replacement with methanol or ethanol and by adding an optimal amount of acetic acid.

The Pd–C (N. E. Chemcat) pretreated with hydrogen in cyclohexane also catalyzes the transamination of pyruvic acid with α-phenylethylamine even more effectively than the Pearlman's catalyst, as seen from the results shown in Table 13.7. When similarly pretreated, the Pd–C (Mozingo) also exhibited considerable activity, although it was less active than Pd–C (N. E. Chemcat) or Pearlman's Pd–C. Similarly to the case with *N*,*N*-diethylbenzylamine, the use of catalyst in ethanol without prereduction in cyclohexane decreased the activities of both Pd–C (N. E. Chemcat) and Pd–C (Mozingo), particularly for the second stage. The very low activity of the latter catalyst for the second stage is in accord with the observation by Hiskey and Northrop that the debenzylation was unsuccessful with the Mozingo's Pd–C. *N*-Debenzylation is involved in the synthesis of an α-hydrazino acid that is useful for the asymmetric synthesis of peptides, starting from an L-α-amino acid (Scheme 13.10).[120] The debenzylation can be performed without racemization in the presence of 1 equiv of *p*-toluenesulfonic acid or hydrochloric acid.

The stereochemistry of hydrogenolysis of carbon–nitrogen bonds has been studied with optically active 2-amino-2-phenylpropionic acid and its derivatives.[85,121,122] Ethyl 2-amino-2-phenylpropionate (**56**, X = NH_2, Y = OEt) was not hydrogenolyzed

TABLE 13.6 Hydrogenolysis of *N,N*-Diethylbenzylamine over Various Pd–C Catalysts[a,b]

Catalyst No.	Catalyst	Solvent for Prereduction[c]	Solvent for Hydrogenolysis	Additive (μmol)[d]	10^3k^e ($mol \cdot min^{-1} \cdot g\ metal^{-1}$)
1	$Pd(OH)_2$–C (Pearlman)[f]	Cyclohexane	+ MeOH[g]	—	135
2		Cyclohexane	MeOH	—	59.0
3		MeOH	(MeOH)[h]	—	110
4		MeOH	MeOH	—	43.2
5		Cyclohexane	+ EtOH	—	95.6
6		Cyclohexane	EtOH	—	62.3
7		EtOH	(EtOH)	—	85.0
8		EtOH	EtOH	—	44.0
9	(Washed with H_2O)[i]	MeOH	MeOH	—	43.7
10	(Washed with H_2O)	EtOH	EtOH	—	45.1
11	(Washed with H_2O)	MeOH	MeOH	AcOH (151)	95.9
12	(Washed with H_2O)	MeOH	MeOH	HCl (55)	20.5
13	Pd–C (N. E. Chemcat)[j]	Cyclohexane	+ MeOH	—	104
14		MeOH	(MeOH)	—	29
15		Cyclohexane	+ EtOH	—	85.6
16		EtOH	(EtOH)	—	61.2
17		Cyclohexane	+ MeOH	AcOH (208)	136
18		Cyclohexane	+ MeOH	HCl (84)	154
19		Cyclohexane	+ MeOH	HCl (220)	55
20	(Washed with H_2O)[k]	Cyclohexane	+ MeOH	—	124
21	*k*	MeOH	(MeOH)	—	17.4
22	*k*	Cyclohexane	+ EtOH	—	102
23	*k*	EtOH	(EtOH)	—	49.5
24	*k*	Cyclohexane	+ MeOH	NaOH (80)	10.7
25	Pd–C (Mozingo)[l]	Cyclohexane	+ MeOH	—	54.6
26	—	MeOH	(MeOH)	—	8.3
27	—	Cyclohexane	+ EtOH	—	51.1
28	—	EtOH	(EtOH)	—	9.2

[a]Nakamura, M.; Nishimura, S. Unpublished results; Nakamura, M. Master's thesis, Tokyo Univ. Agric. Technol. (1990); Nishimura, S.; Higashijima, M. *Hyomen* **1992**, *30*, 645. Reprinted with permission from Hyomen Danwakai & Colloid Konwakai, Japan.

[b]*N,N*-Diethylbenzylamine (0.1 ml, 545 μmol) was hydrogenolyzed with 2–4 mg of catalyst in 1.5 ml solvent at 25°C and 1 atm H_2.

[c]The catalyst was prereduced in the solvent (usually 0.6 ml) at 25°C and 1 atm H_2 for 15 min.

[d]Added after the catalyst had been prereduced.

[e]The rate at an initial stage.

[f]19.3% Pd.

[g]The solvent was further added to the prereduced mixture until the total volume of the solvent became 1.5 ml.

[h]The solvent for prereduction was not replaced.

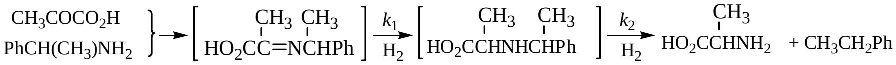
[i]$Pd(OH)_2$–C was washed thoroughly with distilled water until the washings became neutral.

[j]5% Pd.

[k]The catalyst washed with methanol and then with water after prereduction in cyclohexane was dried.

[l]9.2% Pd.

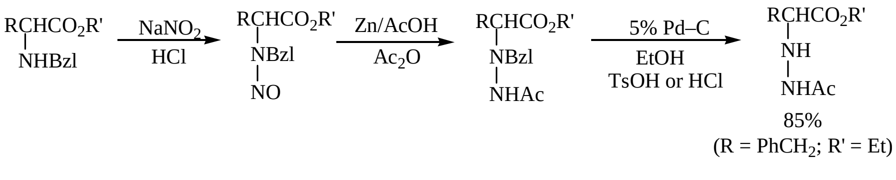
TABLE 13.7 Rates of Hydrogenation of a Mixture of Pyruvic Acid and α-Phenylethylamine over Various Pd–C Catalysts[a,b]



Catalyst	Solvent for Prereduction	Solvent for Hydrogenation	10^4k_1	10^4k_2
			(mol·min−1·g metal−1)	
$Pd(OH)_2$–C	Cyclohexane	+ EtOH	64	16
(Pearlman)[c]	EtOH	+ Cyclohexane	61	13
Pd–C (N. E.	Cyclohexane	+ EtOH	202	22
Chemcat)[d]	EtOH	+ Cyclohexane	154	7.2
Pd–C (Mozingo)[e]	Cyclohexane	+ EtOH	57	5.9
	EtOH	+ Cyclohexane	45	1.0

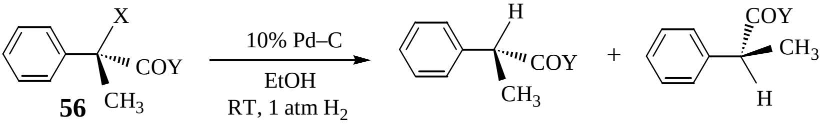
[a]Nakamura, M.; Nishimura, S. Unpublished results; Nakamura, M. Master's thesis, Tokyo Univ. Agric. Technol. (1990).
[b]A mixture of pyruvic acid (0.14 ml, 2 mmol) in 4 ml of cold ethanol and α-phenylethylamine (0.48 ml, 4 mmol) in 4 ml of cold ethanol that had been laid for 30 min was added to the Pd–C (0.3 g) prereduced in the solvent for prereduction. The mixture was hydrogenated at 40°C and 1 atm H_2 in 14 ml of the solvent, which had been adjusted to contain 11 ml of ethanol and 3 ml of cyclohexane.
[c]19.3% Pd.
[d]5% Pd.
[e]9.2% Pd.

but was hydrogenated at the benzene ring over Raney Ni in ethanol at room temperature and atmospheric pressure. No reaction occurred over Pd–C under ordinary conditions. At about 150°C and 6 MPa H_2, most of the aminophenylpropionate underwent hydrogenation to give ethyl 2-phenylpropionate (88%), ethyl 2-cyclohexylpropionate (3%), and ethyl 2-amino-2-cyclohexylpropionate (14%). The optical purity of the product was, however, only 7%, with retained product in excess.[121] The hydrogenolysis of 2-dimethylamino-2-phenylpropionic acid (**56**, X = NMe_2, Y = OH), its methyl and ethyl esters, and its amide over a Pd–C in ethanol proceeded much more readily at room temperature and atmospheric pressure with 72–99% inversion of configuration.[122] The hydrogenolysis of ethyl 2-dimethylamino- and 2-methylamino- 2-phenylpropionates (**56**, X = NMe_2 and NHMe; Y = OEt) over Raney Ni also proceeded with inversion of configuration.[123] The quaternary ammonium salt obtained by methyla-



Scheme 13.10 Synthesis of α-hydrazino acids from α-amino acids.

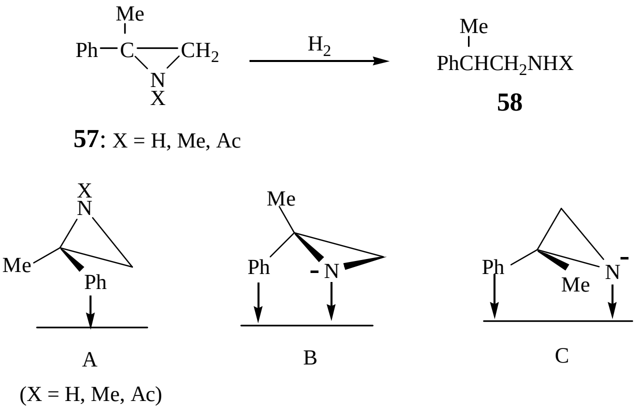
tion of the methyl ester (**56**, X = NMe_3^+, Y = OMe) was hydrogenolyzed most rapidly over Pd–C, and methyl 2-phenylpropionate produced was largely racemized. 2-Anilino-2-phenylpropionic acid (**56**, X = NHPh, Y = OH) was hydrogenolyzed with inversion of configuration over both Pd–C and Raney Ni.[122,123] The hydrogenolysis of its methyl ester over Raney Ni, however, proceeded with retention of configuration. The results by Dahn et al. with 10% Pd–C as catalyst are shown in eq. 13.59.



(13.59)

X	Y	Optical purity (%)	Product with inversion (%)
NH_2	OH	—	—
NH_2	OMe	—	—
NHCHO	OH	—	—
$NHCOCH_3$	OEt	—	—
NMe_2	OH	98	99
NMe_2	OMe	45	72
NMe_2	OEt	59	79
NMe_2	NH_2	67	84
NMe_3^+	OMe	0	50
NHPh	OH	>31	>66

The stereochemistry of hydrogenolysis of optically active 2-methyl-2-phenylaziridine (**57**, X = H) has been studied by Mitsui and Sugi.[124,125] The products were mostly 2-phenyl-l-propylamine (**58**, X = H)) (92–100%), along with small amounts of 2-phenyl-2-propylamine or 2-cyclohexypropylamine (0–7%) and hydrocarbons (2-phenylpropene or -propane) (~0–5%). Over $Pd(OH)_2$ in ethanol, the configuration of **58** (X = H) was predominantly of inversion, while over platinum oxide it was largely retained. With addition of NaOH to palladium, however, the retained product



Scheme 13.11 Hydrogenolysis of 2-methyl-2-phenylaziridine and its *N*-derivatives.

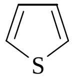
increased with increasing amount of the additive. Such an influence of NaOH was not observed with the *N*-methyl and *N*-acetyl derivatives of **57** (X = Me and Ac, respectively), which gave always the inverted products predominantly. The effect of NaOH on **58** (X = H) has been explained by the formation of an anion on the nitrogen atom that may be adsorbed strongly to the catalyst surface. Thus, it has been suggested, as illustrated in Scheme 13.11, that **58** (X = H) in the absence of NaOH and its *N*-methyl and *N*-acetyl derivatives are hydrogenolyzed in the adsorbed state A, while in the presence of NaOH **58** (X = H) is hydrogenolyzed in the adsorbed states B or C. Hydrogenolysis of **57** (X = H) over Raney Ni and Raney Co resulted in low optical activities (23 and 14%, respectively), with retained product in excess.

13.3 HYDROGENOLYSIS OF ORGANIC SULFUR COMPOUNDS

Hydrogenolysis of carbon–sulfur bonds is a widely utilized reaction for removing sulfur from sulfur-containing organic compounds, and is known as desulfurization or hydrodesulfurization. Bougault et al. used Raney Ni for the first time for the desulfurization of aliphatic thioalcohols and disulfides in neutral and alkaline solution.[126] Since then the reaction has been widely applied, for example, for organic syntheses, purification of solvents and substrates, structural studies, and determination of sulfur contents.[127]

The hydrogenolysis of sulfur-containing compounds is also an important industrial process, known as *hydrodesulfurization*, in the field of petroleum refinery to reduce the sulfur content of petroleum fractions. The most commonly used catalyst is a mixture of either cobalt or nickel and molybdenum oxides supported on alumina, which is sulfided before use and usually employed at about 300–400°C and 1–7 MPa H_2.[128] The basic reactions involved in the hydrodesulfurization process are represented in eq. 13.60.

$$\text{R–S–S–R'} + 3\text{H}_2 \longrightarrow \text{RH} + \text{R'H} + 2\text{H}_2\text{S}$$
$$\text{R–SH} + \text{H}_2 \longrightarrow \text{RH} + \text{H}_2\text{S}$$
$$\text{R–S–R'} + 2\text{H}_2 \longrightarrow \text{RH} + \text{R'H} + \text{H}_2\text{S} \qquad (13.60)$$

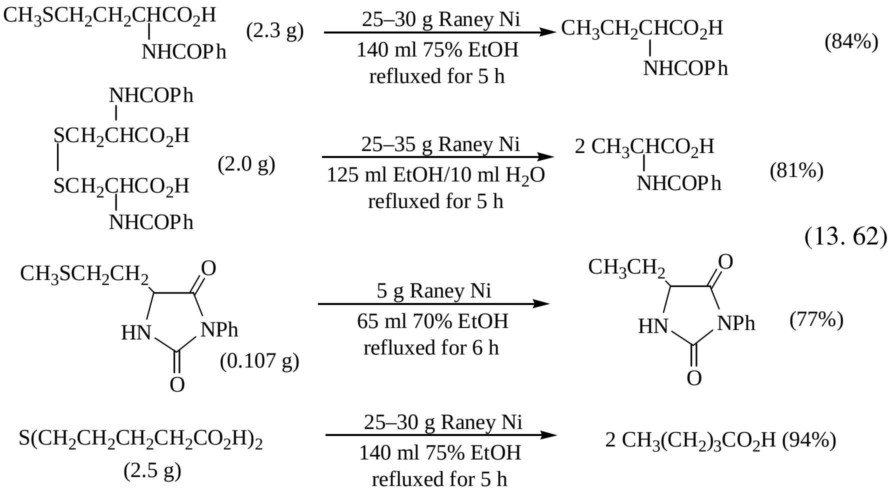


$$+ 3\text{H}_2 \longrightarrow \text{C}_4\text{H}_8 \text{ (a mixture of isomers)} + \text{H}_2\text{S}$$

The reaction of a sulfide with Raney Ni may follow two simultaneous courses as shown in eq. 13.61.[129,130] The source of hydrogen may be that associated with Raney Ni or the hydrogen produced by dehydrogenation of a solvent such as ethanol.[131] According to Bonner, however, dehydrogenation of ethanol to acetaldehyde and hydrogen is merely a concurrent reaction.[132]

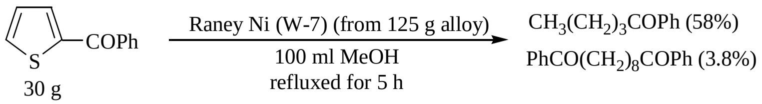
$$\text{R–S–R'} + \text{Raney Ni (H)} \begin{cases} \xrightarrow{\textbf{(a)}} \text{RH} + \text{R'H} \\ \xrightarrow{\textbf{(b)}} \text{R–R} + \text{R–R'} + \text{R'–R'} \end{cases} \qquad (13.61)$$

Whether the alkyl groups are combined with hydrogen or with each other may depend on the amount of hydrogen available. Use of a deactivated or degassed catalyst favors formation of dimeric products, while use of active Raney Ni in large amounts leads to high yields of hydrogenated products. Mozingo et al. treated aliphatic and aromatic sulfides, disulfides, sulfoxides, and sulfones with large amounts of Raney Ni (W-2, but developed at 80 or 50°C for 1 h), usually in boiling ethanol.[129] Under these conditions, the products by reaction course (**a**) in eq. 13.61 were obtained in yields of 65–95% of the theoretical amount. Thus, toluene was obtained in an 85% yield from benzyl sulfide. Benzoylmethionine, benzoylcystine, methionine phenylhydantoin, and δ,δ′-thiodivaleric acid gave the corresponding desulfurized compounds in high yields as shown in eq. 13.62. Diphenyl sulfide and *p*-tolyl disulfide were converted into benzene and toluene, respectively, in 68% and 87% yield. Diphenyl sulfoxide and diphenyl sulfone gave benzene in 75 and 65% yields, respectively. The reaction of γ-methylthiobutyric acid in refluxing methanol, instead of refluxing ethanol was carried out quite as well to give 95% of butyric acid. Treatment of 2-benzoylthiophene with active W-7 Raney Ni in refluxing methanol led mostly to the hydrodesulfurized product, and formation of the dimeric product by the reaction course (**b**) was at a low level (eq. 13.63) However, with a deactivated catalyst, the yield of valerophenone decreased to 47% and the yield of dibenzoyloctane increased to 4.4%.[133]



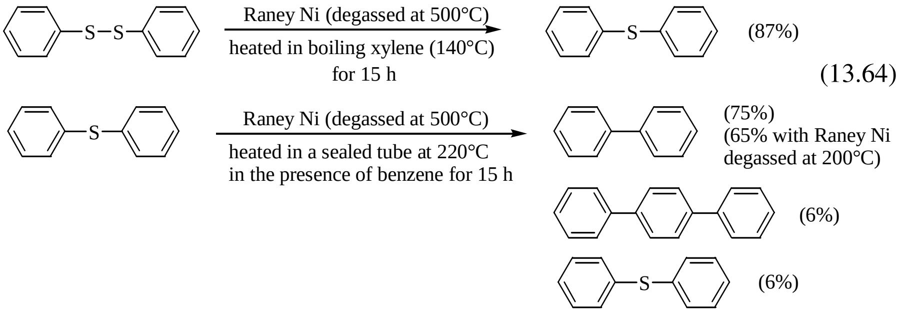
(13. 62)

Hauptmann et al. found that aromatic disulfides, thioesters, and thiols were transformed into thioethers when refluxed in xylene (140°C) in the presence of Raney Ni degassed at 200°C.[130,134,135] However, when these compounds were heated at 220°C with degassed Raney Ni or reduced Ni, biphenyls were obtained in good yields. The yields of the products with Raney Ni degassed at 500°C were never lower and were sometimes higher than those obtained with Raney Ni degassed at 200°C, as seen from an example shown in eq. 13.64. On the basis of these results, it was concluded that the presence of hydrogen was not essential for these desulfurizations.[136]



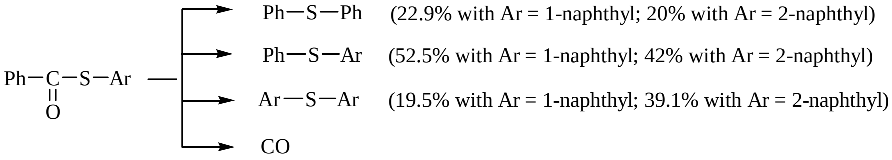
(13.63)

When aryl thiobenzoates were treated with Raney Ni degassed at 200°C in refluxing xylene, mixed thioethers were the main products among the three possible thioethers (see Scheme 13.12). The production of carbon monoxide was confirmed by heating 1-naphthyl thiobenzoate with the degassed Raney Ni at 140°C in a stream of nitrogen.[134] The Raney Ni used for desulfurization is strongly combined with sulfur to form nickel sulfide. By liberating hydrogen sulfide from the nickel sulfide with an acid, this reaction may be utilized for the determination of microgram quantities of sulfur contained in organic compounds.[137,138] By applying this method, Granatelli



(13.64)

demonstrated that as little as 0.1 ppm of organically bound sulfur present in nonolefinic hydrocarbon solutions was determinable for a maximum recommended sample size of 50 g. It was noted that olefins present in the sample, even at 2% concentration, introduced appreciable error.[138] Treatment with Raney Ni also provides an effective method to purify solvents or aromatic compounds for hydrogenation, by removing sulfur compounds, which may become powerful catalyst poisons in hydrogenation.[139] In a vapor-phase dehydrogenation of cyclohexane over Pt–Al_2O_3 at 200°C and 0.1 MPa, the degree of deactivation of the catalyst decreased to one-third in > 20-h opera-



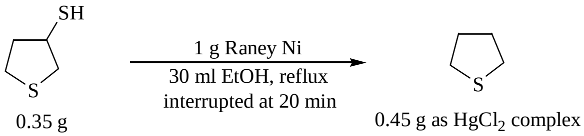
Scheme 13.12 Formation of thioethers from aryl thiobenzoates in refluxing xylene in the presence of Raney Ni degassed at 200°C.

tion when the starting cyclohexane, containing 5.58 ppb (parts per billion) sulfur, had been pretreated with Raney Ni.[140]

The desulfurization of organic sulfur compounds with Raney Ni using far greater amounts than a catalytic is not a *catalytic* hydrogenolysis in the strict sense but involves a stoichiometric chemical reaction, since the catalyst itself is converted into nickel sulfide. However, since it has found many useful applications with Raney Ni (a hydrogenation catalyst), this reaction has been treated in this section.

13.3.1 Thiols

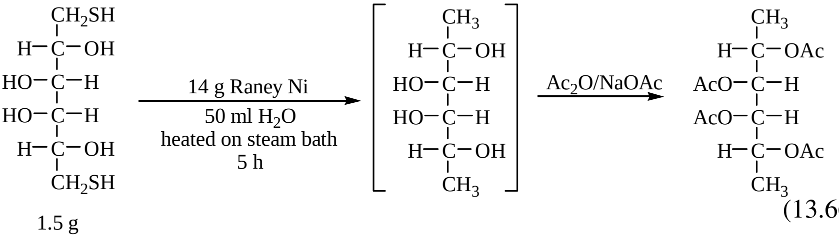
Thiols are more readily hydrogenolyzed than thioethers by treatment with Raney Ni to give the corresponding desulfurized products. For example, 3-mercaptotetrahydrothiophene was selectively desulfurized to tetrahydrothiophene when the reaction was interrupted at an appropriate time that was indicated by estimation of thiol values (eq. 13.65).[141]



(13.65)

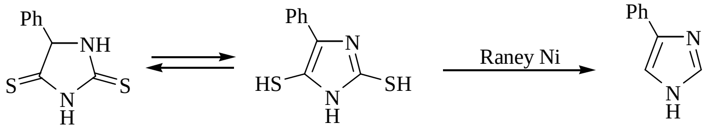
Bonner showed that 2-thionaphthol was desulfurized to naphthalene nearly quantitatively with Raney Ni in refluxing ethanol as well as in refluxing benzene, while 2-naphtyl disulfide was obtained in 50% yield with the Raney Ni degassed at 200°C in refluxing ethanol.[132] These results indicate that the hydrogen associated with Raney Ni is essential for the desulfurization under the conditions employed, and the hydrogen formed by dehydrogenation of ethanol to acetaldehyde does not play an important role.[132]

Thiol derivatives of carbohydrates were desulfurized with Raney Ni without complication. For example, 1,6-dithiodulcitol was desulfurized to 1,6-dideoxydulcitol in aqueous solution with Raney Ni, and acetylation of the product gave tetraacetyl-1,6-dideoxydulcitol (eq. 13.66).[142]



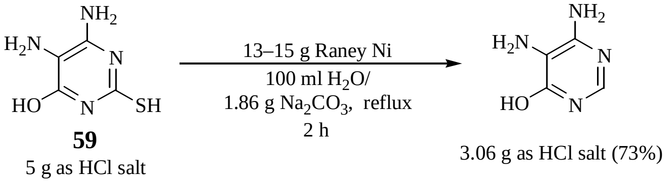
(13.66)

4-Phenylimidazole was synthesized by treatment with Raney Ni of the corresponding thiohydantoin derivative. This desulfurization was considered to take place via the tautomeric dimercaptoimidazole, as shown in eq. 13.67.[143]

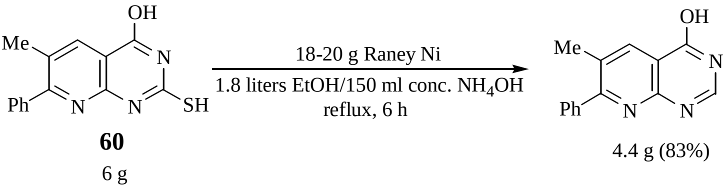


(13.67)

The mercapto group in pyrimidine derivatives **59** and **60** was desulfurized successfully in the presence of amino and/or hydroxyl groups (eqs. 13.68[144] and 13.69[145]).

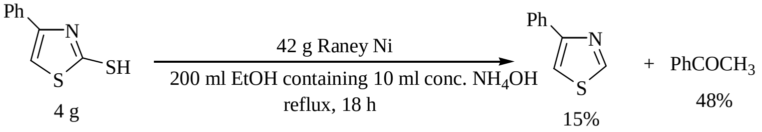


(13.68)

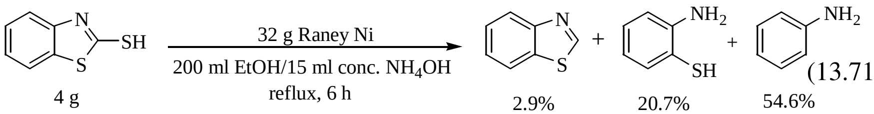


(13.69)

On the other hand, the reaction of mercarptothiazoles with Raney Ni usually gives the thiazoles only in small amounts, and the predominant products are those desulfurized not only at the mercapto group but also at the thiazole ring, as seen from the examples shown in eqs. 13.70 and 13.71.[146] The Raney Ni used in these equations was prepared by a procedure similar to that for W-4 but developed at a lower temperature, and appeared to have a much greater amount of adsorbed hydrogen than did W-2 or W-4.[147]



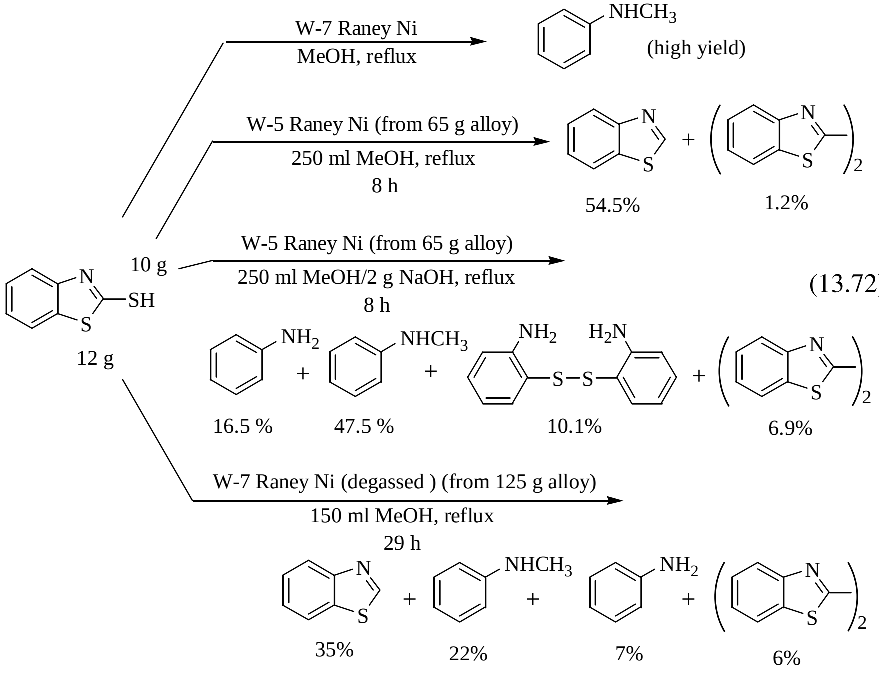
(13.70)



(13.71)

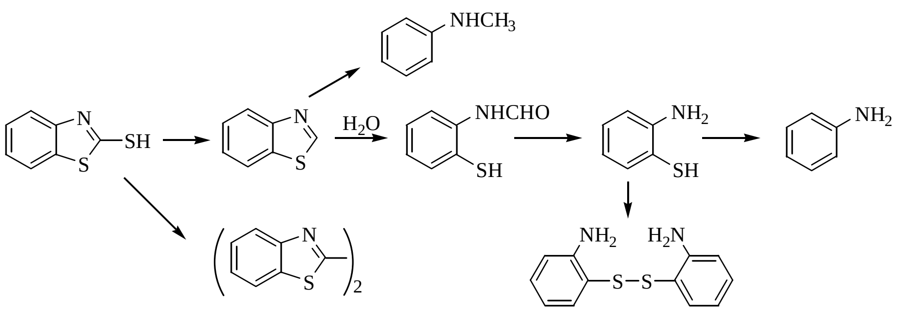
Badger and Kowanko studied the desulfurization of thiazoles with various preparations of Raney Ni.[148] Benzothiazoles were desulfurized to secondary amines in excellent yields by treatment with very active W-6 or W-7 Raney Ni in boiling methanol. In neutral solvent, W-5 Raney Ni was relatively less active. However, in the presence of alkali, ring fission followed by desulfurization occurred to give aniline, *N*-methylaniline, and *o*-aminothiophenol or *o*-aminodiphenyldisulfide. With a partially degassed W-7 Raney Ni in refluxing methanol, benzothiazole was obtained in 35% yield

from 2-mercaptobenzothiazole, along with other products.[148] Equation 13.72 summarizes the reactions of 2-mercaptobenzothiazole with various Raney Ni catalysts.



(13.72)

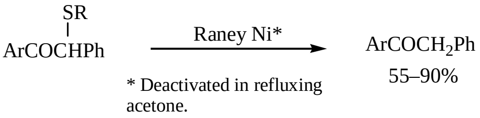
With the very active W-6 or W-7 Raney Ni (alkaline), desulfurization occurs before ring fission and *N*-methylaniline is the only product, while with less active W-5 and degassed W-7 Raney Ni in the presence of alkali, ring fission takes place to some extent before desulfurization , which may lead to *o*-aminothiophenol (isolated in its oxidized form, 2,2′-diaminodiphenyl disulfide) and aniline, probably via the formyl derivative as the intermediate as shown in Scheme 13.13.[148]



Scheme 13.13 Reaction pathways of 2-mercaptobenzothiazole in the presence of Raney Ni in refluxing methanol.

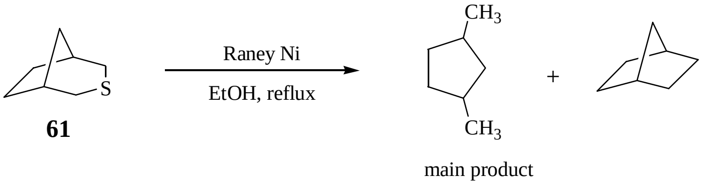
13.3.2 Thioethers

The alkylthio group in an aromatic ketone may be removed with Raney Ni without affecting the carbonyl group. Thus, treatment of desyl thioethers (α-alkylthiodesoxybenzoins) with Raney Ni, which had been deactivated by refluxing in acetone,[149] gave desoxybenzoins in yields of 55–90% (eq. 13.73).[150]



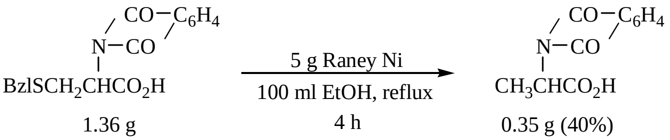
(13.73)

Desulfurization of cyclic thioether **61** is accompanied by formation of ring-closed bicyclo[2.2.1]heptane besides 1,3-dimethylcyclopentane as the main product (eq. 13.74).[151] As noted before, such carbon–carbon bond formation accompanying desulfurization occurs more readily over degassed Raney Ni, even with acyclic thioethers (see eq. 13.64).



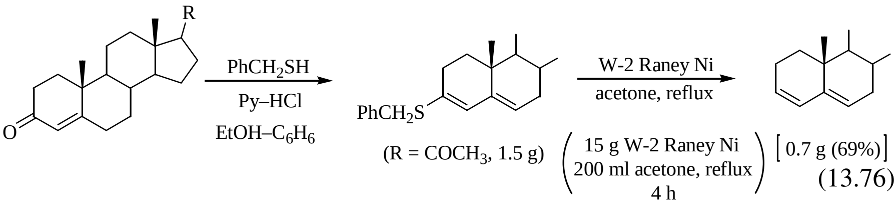
(13.74)

L-Cysteine was transformed into optically active α-alanine derivative as *S*-benzyl-*N*-phthaloyl derivative by desulfurization with Raney Ni (eq. 13.75).[152]

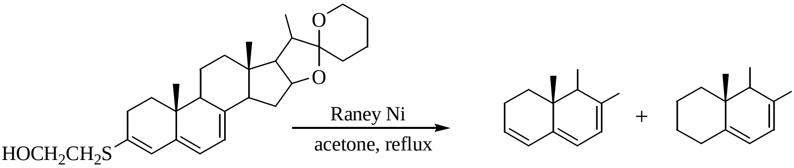


(13.75)

Benzylthioenol ethers of Δ^4-3-oxo steroids, which are easily obtained by reaction of Δ^4-3-oxo steroids with benzyl mercaptan in the presence of pyridine hydrochloride, can be desulfurized to $\Delta^{3,5}$-dienes with deactivated Raney Ni in refluxing acetone without affecting the conjugated diene system (eq. 13.76).[153,154] Desulfurization with active W-2 Raney Ni in refluxing dioxane or ethanol, the thioenol ethers of testosterone and cholestenone gave the corresponding saturated compounds. The benzylthioenol ether group is stable toward lithium hydride reduction and has been employed to protect the 3-oxo-4-ene moiety in the lithium aluminum hydride reduction of a 17- or 20-oxo group. Desulfurization of a similar thioenol ether of 3-oxo-$\Delta^{4,6}$ steroid, however, is accompanied by formation of a partially hydrogenated product (eq. 13.77).[155]



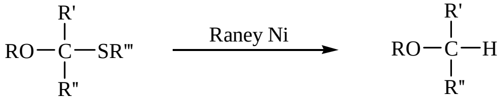
(13.76)



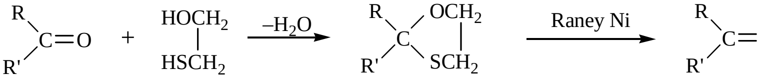
(13.77)

13.3.3 Hemithioacetals

Hemithioacetals may be transformed in two ways with Raney Ni. The sulfur group may be removed with the oxygen group intact as in eq. 13.78 or desurfurized to recover the parent carbonyl compounds. In the ethylenehemithio acetal of a ketone, since the oxo group can be recovered by treatment with Raney Ni, this reaction makes it possible to use the hemithio acetal as a protective group for the carbonyl group (eq. 13.79).

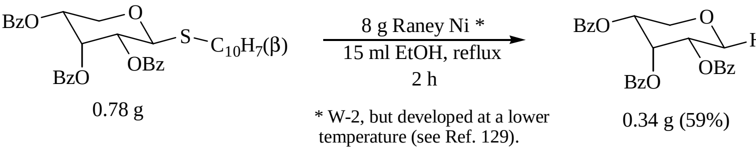


(13.78)



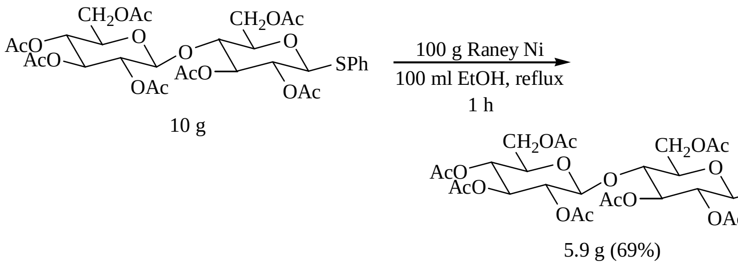
(13.79)

Desulfurization of a hemithio acetal as in eq. 13.78 has often been utilized in carbohydrate chemistry. As an example, 2′-naphthyl 1-thio-β-D-ribopyranoside tribenzoate was converted to 2,3,4-tribenzoyl-1,5-anhydroribitol in a good yield (eq. 13.80).[156] The desulfurization may be performed without protecting the alcoholic hydroxyl groups.[157,158]



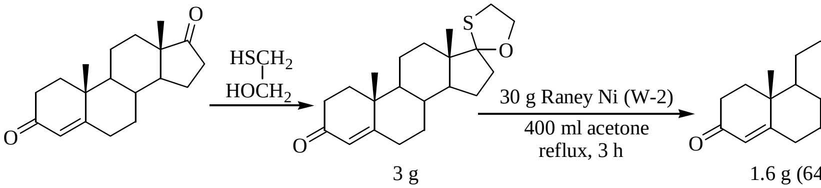
(13.80)

Equation 13.81 shows an example of similar desulfurization with a disaccharide derivative, phenyl 1-thio-β-cellobioside heptaacetate.[159]



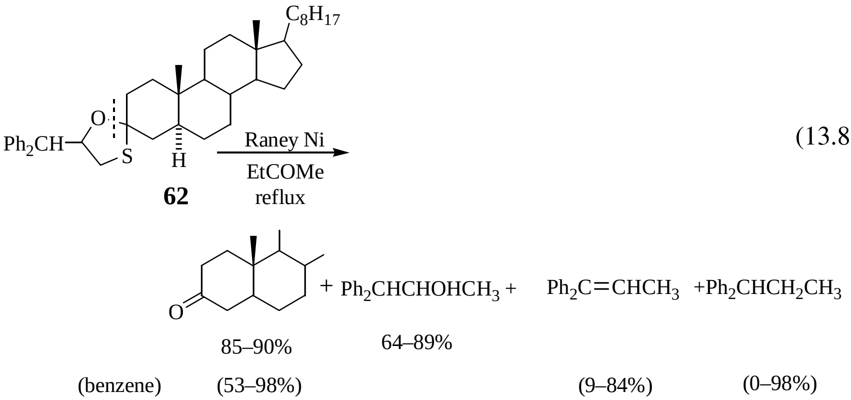
(13.81)

4-Androstene-3,17-dione can be transformed selectively into the 17-ethylenehemithio acetal in the presence of the α,β-unsaturated carbonyl system. The parent androstenedione can be regenerated by treatment of the hemithio acetal with Raney Ni (eq. 13.82) by the reaction of eq. 13.79.[160]

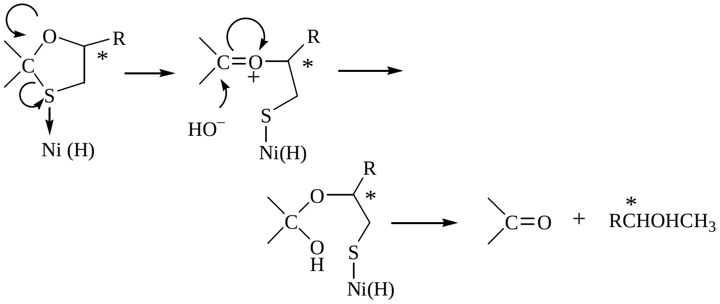


(13.82)

The Raney Ni desulfurization of cyclic 5-membered hemithioactals (1,3-oxathiolanes) in acetone or ethyl methyl ketone to yield the corresponding ketones has been shown to involve an introduction of oxygen from a source other than the 1,3-oxathiolane oxygen.[161,162] The principal products from desulfurization of a hemithio acetal of cholestan-3-one, spiro-(5-benzhydryl-1,3-oxathiolane-2,3′-cholestane) (**62**), were cholestan-3-one and 1,1-diphenylpropan-2-ol (eq. 13.83). The complete retention of optical activity in the 1,1-diphenylpropan-2-ol formed also suggested that the dotted bond in **62** has undergone scission during the desulfurization step.



(13.83)



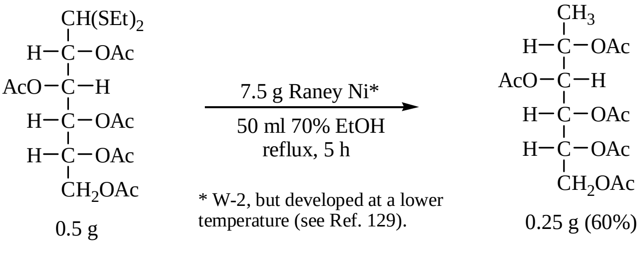
Scheme 13.14 A possible mechanism for regeneration of ketone from an ethylenehemithio acetal by treatment with Raney Ni.

Djerrassi and co-workers suggested a mechanism for the oxygen introduction step, which involved formation of a hemiacetal intermediate caused by the fission of the carbon–sulfur bond followed by attack with hydroxide ion, as illustrated in Scheme 13.14.[161,162] The mechanism is supported by the preservation of chiral center when an optically active ethylenehemithio acetal was subjected to desulfurization to regenerate the ketone.

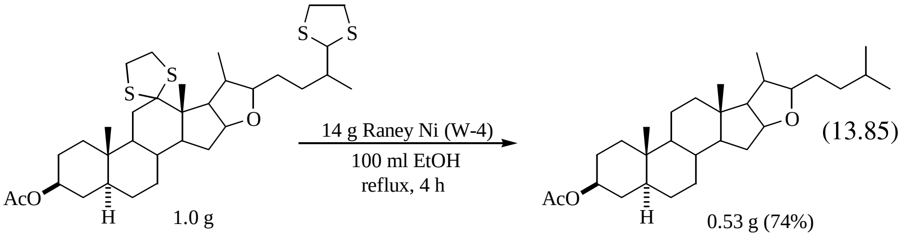
On the other hand, when the reaction was performed in benzene under anhydrous conditions, the chief products were cholestan-3-one (up to 98%) and a mixture of 1,1-diphenylpropane and 1,1-diphenyl-1-propene, the proportion of which depended on the age of the catalyst (see eq. 13.83). For the reaction in benzene solution, a mechanism that involves a 1,4-diradical intermediate has been suggested.

13.3.4 Dithioacetals

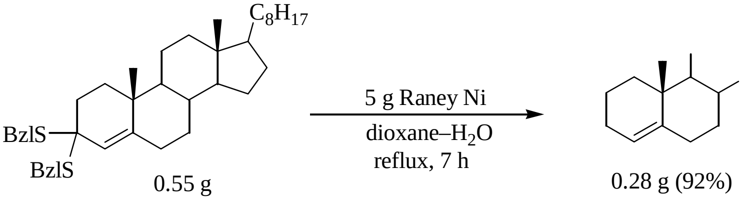
Dithioacetals of aldehydes and ketones are transformed to the corresponding methylene compounds by treatment with Raney Ni. This transformation may be used in place of the methods known as *Clemmensen* or *Wolff–Kishner reduction*. The method using Raney Ni is advantageous in that the reaction can be performed under a neutral condition. Typical examples are given in eqs. 13.84,[131] 13.85,[163] and 13.86.[164] In the example in eq. 13.86, desulfurization afforded a high yield of 4-cholestene without affecting the Δ^4 double bond.



(13.84)



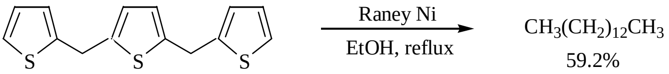
(13.85)



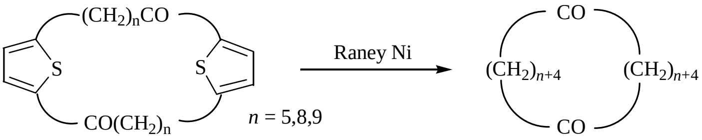
(13.86)

13.3.5 Thiophenes

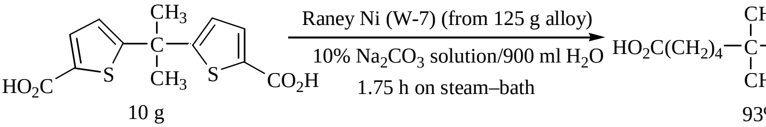
Thiophenes are desulfurized to give products with a C_4 carbon chain (see eqs. 13.60 and 13.63), and hence the desulfurization of thiophene derivatives has been applied for syntheses of compounds with longer alkyl chains, in particular, for long-chain compounds, which are not easily obtainable by conventional synthetic methods. Examples are shown in eqs. 13.87–13.90.



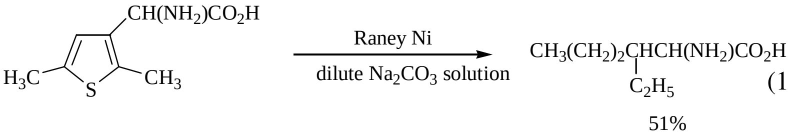
(13.87)[165]



(13.88)[166]



(13.89)[167]

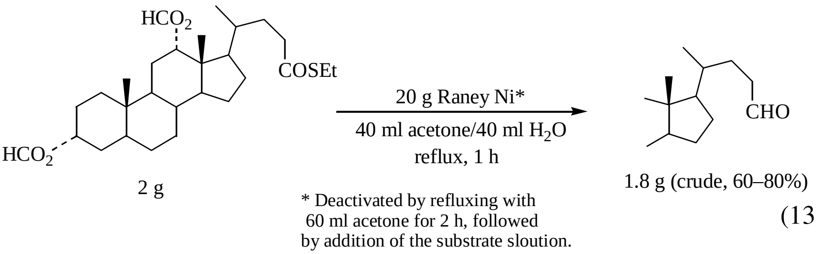


(13.90)[168]

13.3.6 Thiol Esters and Thioamides

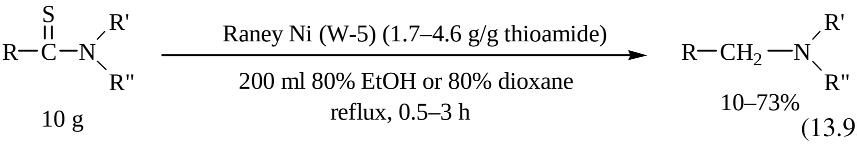
Thioesters are cleaved primarily with Raney Ni between the sulfur atom and the alkyl or aryl group. With Raney Ni degassed at 200°C in refluxing xylene, aryl thiobenzoates give aryl thioethers (see Scheme 13.12).[134] Cleavage of the sulfur–carbonyl carbon bond may lead to an aldehyde or alcohol (eq. 13.91). Good yields of aldehydes were obtained with Raney Ni deactivated by heating in boiling acetone. An example is shown in eq. 13.92.[149]

(13.91)



(13.92)

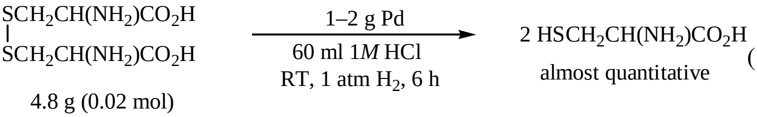
The thiocarbonyl group in thioamides can be transformed into amines by treatment with Raney Ni (W-5) (eq. 13.93).[169] The transformation could be effected even at room temperature.



(13.93)

13.3.7 Disulfides

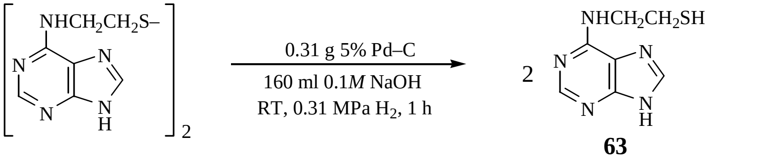
Bergmann and Michalis have shown that L-cystine (eq. 13.94) and dialanyl-L-cystine can be hydrogenated to the corresponding cysteines over palladium black in acidic medium. These hydrogenations, however, were unsuccessful with platinum as catalyst.[170] L-Cystine dimethyl ester dihydrochloride was similarly hydrogenated to the thiols with a palladium black in methanol solution at 24°C and atmospheric hydrogen pressure.[171] Di(*p*-nitrocarbobenzyloxy)-L-cystine was hydrogenated to L-cysteine in aqueous alkaline solution over 10% Pd–C (see eq. 13.29a).[63]



(13.94)

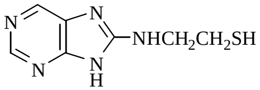
Johnston and Gallagher obtained 2-(purin-6-ylamino)ethanethiol (**63**) (eq. 13.95), 2-(purin-8-ylamino)ethanethiol (**64**), and 2-(2-pyrimidinylamino)ethanethiol (**65**) by

facile hydrogenolysis of the corresponding disulfides over 5% Pd–C in basic media.[172] Similar catalytic hydrogenolysis, however, was unsuccessful to yield the benzothiazole derivative **66**.

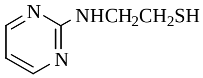


1.55 g (4 mmol) → **63** 0.99 g (64%)* (13.95)

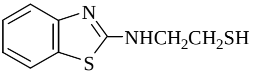
* A 2-h hydrogenolysis on a 20-mmol scale gave an 80% yield.



64



65



66

13.3.8 Hydrogenolysis over Metal Sulfide Catalysts

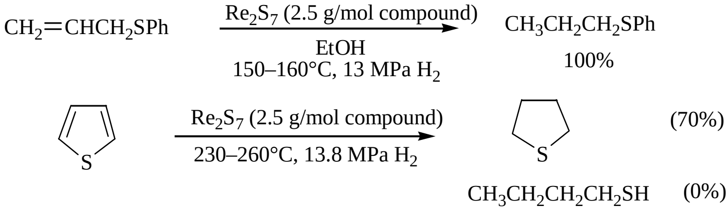
Metal sulfide catalysts such as rhenium heptasulfide (Re_2S_7) and molybdenum trisulfide (MoS_3) have been shown to be effective for selective hydrogenolysis of sulfur-containing compounds at high temperatures and pressures. Broadbent et al. obtained thiophenol quantitatively by hydrogenolysis of diphenyl disulfide over Re_2S_7 in methylcellosolve at 165–195°C and 15 MPa H_2.[173] Itabashi studied the hydrogenation of various disulfides over MoS_3 as catalyst.[174–176] Both dialkyl disulfides and diaryl disulfides were hydrogenolyzed at the S–S linkage to give the corresponding thiols and thiophenols in high yields at 130–140°C. Further hydrogenolysis took place at 300°C for dialkyl disulfides to give alkanes and for diphenyl disulfide to give benzene. For example, didodecyl disulfide was hydrogenated to dodecanethiol in more than 92% yields at 120–200°C (eq. 13.96) and hydrogenolysis to dodecane took place at temperatures higher than 250°C.[176]

$$\underset{40.2\text{ g }(0.1\text{ mol})}{(C_{12}H_{25}S\text{–})_2} \xrightarrow[150°\text{C},\ 10.7\text{ MPa } H_2,\ 0.75\text{ h}]{1.9\text{ g } MoS_3} \underset{95.9\%}{2\ C_{12}H_{25}SH} \qquad (13.96)$$

In the case of dibenzyl disulfide, the hydrogenolysis of the second stage to give toluene occurred at a lower temperature (200°C), as might be expected from the high reactivity of benzyl-type compounds. The hydrogenolysis of dithioglycolic acid proceeded at somewhat lower temperatures. The resulting thioglycolic acid tended to subject further hydrogenolysis to give acetic acid at much lower temperatures (almost complete conversion at 180°C) than the usual disulfides. The product, therefore, was mixed with acetic acid, resulting in lower yields of thioglycolic acid (64.3% maximum yield at 130°C and 5 MPa H_2) (eq. 13.97).[175] On the other hand, β-dithiodipropionic acid gave high yields of β-mercaptopropionic acid, similar to those of the usual disulfides.

$$\begin{array}{l} SCH_2CO_2H \\ | \\ SCH_2CO_2H \end{array} \xrightarrow[\substack{110\text{–}130°C \\ 5\ MPa\ H_2}]{MoS_3} \underset{64.3\%\ \text{max. yield}}{2\ HSCH_2CO_2H} \xrightarrow[130\text{–}180°C]{} CH_3CO_2H \qquad (13.97)$$

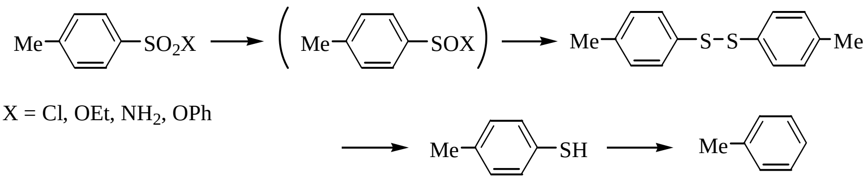
Over MoS_3, alkyl and aryl thioethers are hydrogenolyzed to give hydrocarbons, via the formation of thiols and hydrocarbons, at temperatures not exceeding 300°C.[177,178] Diphenyl sulfide was converted to benzene over Re_2S_7 in ethanol at 300°C.[173] However, thioethers appear to be stable at the temperatures of 155–245°C over Re_2S_7, since hydrogenation of allyl phenyl sulfide and thiophene over Re_2S_7 affords exclusively propyl phenyl sulfide at 150–160°C and thiolane at 230–260°C, respectively (eq. 13.98).[173]



(13.98)

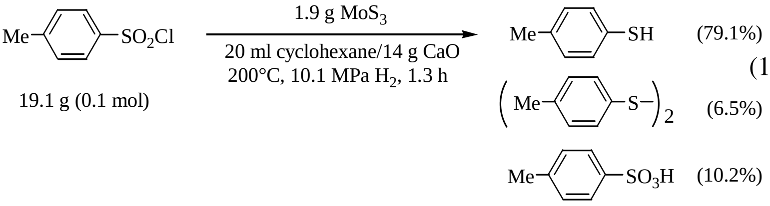
13.3.9 Sulfones, Sulfonic Acids, and Their Derivatives

The hydrogenolysis of sulfones and sulfonic acids over MoS_3 requires higher temperatures (300–375°C) than for thiols, sulfides, or disulfides, except with dibenzyl sulfone, where hydrogenolysis to give toluene proceeded at 200–250°C.[179,180] *p*-Toluenesulfonic acid derivatives (*p*-$MeC_6H_4SO_2X$, where X = Cl, OEt, NH_2, OPh) were hydrogenolyzed at lower temperatures than required for *p*-toluenesulfonic acid. The temperature required increased with respect to X in the order Cl < OEt < NH_2 < OPh. The phenyl ester was cleaved almost completely to toluene at 300°C. Di-*p*-tolyl disulfide and *p*-thiocresol were obtained as intermediates in these reactions. From the results, the reaction sequence shown in Scheme 13.15 has been suggested for the hydrogenation of *p*-toluenesulfonic acid derivatives.[181] *p*-Toluenesulfonyl chloride could be transformed to *p*-toluenethiol in 79.1% yield by hydrogenation over MoS_3 in cyclohexane at 200°C and 10 MPa H_2 in the presence of calcium oxide to depress the hydrolysis of the chloride to the sulfonic acid (eq. 13.99).[182] In the absence of cal-



Scheme 13.15 Hydrogenolysis of *p*-toluenesulfonic acid derivatives leading to toluene over MoS_3.

cium oxide, the formation of the sulfonic acid amounted to more than 40%, and the yield of the reduction products was lower than 50%.

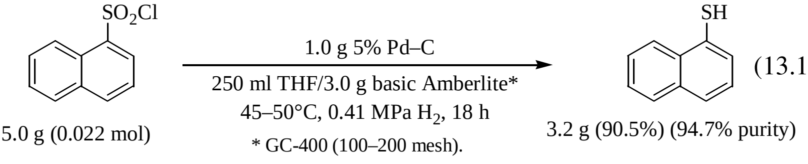


(13.99)

Over palladium catalysts in acetone–water, arenesulfonyl chlorides are converted to the corresponding sulfinic acids, and further slowly to diaryl disulfide (eq. 13.100).[183,184]

$$\mathrm{Ar{-}SO_2Cl} \xrightarrow[\text{acetone/H}_2\text{O}]{\text{Pd}} \mathrm{Ar{-}SO{-}OH} \xrightarrow{\text{slow}} (\mathrm{ArS})_2 \qquad (13.100)$$

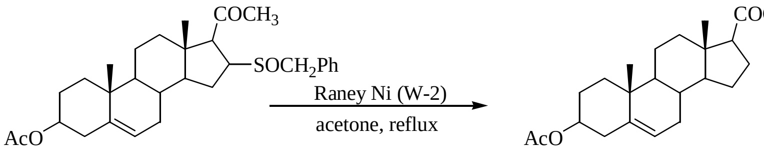
Mylroie and Doles were successful to hydrogenate aromatic sulfonyl chlorides to thiols using 5% Pd–C in a solvent such as tetrahydrofuran containing a mild base such as *N*,*N*-dimethylacetamide to neutralize the strong acid formed.[185] Hydrogenation in the presence of a strongly basic Amberlite resin was also effective as seen in an example shown in eq. 13.101, although in some cases large amounts of the disulfides were formed when the resin was used or when no base was used. The disulfides formed could be hydrogenolyzed to the thiols by use of Raney Co at slightly elevated temperature (63°C) under 3.4 MPa H_2.



(13.101)

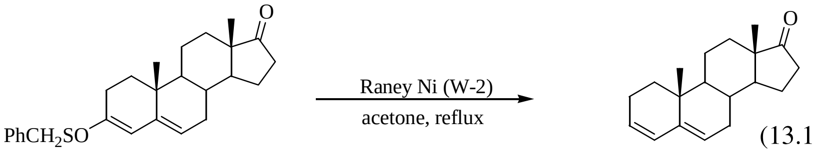
Sulfones are usually resistant to desulfurization with Raney Ni.[151,186] However, diphenyl sulfone[129] and benzyl-type sulfones[187] are desulfurized with the use of large excess amounts of Raney Ni. Benzyl sulfones undergo desufurization markedly more rapidly than do phenyl sulfones in ethanol, and more slowly in benzene than in ethanol.[188] Like sulfones, sulfonic acids are also unreactive toward desulfurization with Raney Ni. However, benzenesulfonic acid and naphthalene-2-sulfonic acid could be desulfurized to give the parent hydrocarbons by the Schwenk–Papa method using Raney alloy and aqueous sodium hydroxide.[189] Treatment of an alkyl *p*-tolenesulfonate with a massive quantity of Raney Ni in ethanol yields an alcohol, together with toluene, while an aryl *p*-toluenesulfonate gives the aromatic hydrocarbon resulting from the hydrogenolysis of the aryl–OTs bond in ethanol at 25°C and 1 atm H_2 (see eq. 13.53).[99]

Sulfoxides can be desulfurized successfully by Raney Ni. The sulfoxido ketone **67** and the sulfoxidoenol ether **69** were readily desulfurized with Raney Ni to yield the ketone **68** and the diene **70**, respectively (eqs. 13.102 and 13.103).[154]



(13.102)

67 **68** 75%

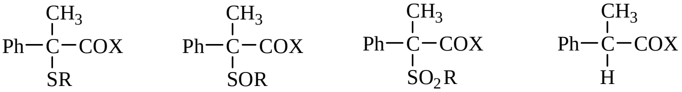


(13.103)

69 **70** 58%

13.3.10 Stereochemistry of the Desulfurization with Raney Nickel

Bonner et al. have found that desulfurization of optically active benzyl-type phenyl sulfide **71a**[187] and phenyl sulfoxide **72a**[190] with Raney Ni always results in completely racemized products **74**. On the other hand, optically active benzyl-type phenyl sulfone **73a** was desulfurized with predominant inversion of configuration in ethanol but with predominant retention in acetone, although the ratios of inversion to retention depended on the conditions of pretreating the catalyst.[187,188] These results clearly indicated that the sulfone **73a** did not undergo desulfurization via **71a** or **72a** as intermediate. Benzyl sulfones **73b** was desulfurized markedly more rapidly than phenyl sulfone **73a** and with predominant retention of configuration in both ethanol and acetone.[188] Imaizumi obtained substantially the same results in the desulfurization of the esters **71c–71e**, **73c**, and **73d** with Raney Ni in ethanol.[191] A free radical cleavage of the carbon–sulfur bonds has been suggested for the racemization with the sulfides and sulfoxides, while a mechanism involving S_N2 (or S_Ni) replacement, which is dependent on the structure and the surface hydrogen availability, has been discussed for the results with the sulfones.[188,191]



71 **72** **73** **74**

a: R = Ph, X = NH_2
b: R = CH_2Ph, X = NH_2
c: R = Ph, X = OEt
d: R = C_6H_4Me, X = OEt
e: R = Et, X = OEt

13.4 HYDROGENOLYSIS OF CARBON–HALOGEN BONDS

The catalytic hydrogenolysis of organic halides, also known as *dehalogenation* or *hydrodehalogenation*, is an important reaction frequently used in organic synthesis.[192] Hydrogen halides produced by hydrogenolysis often poison the catalysts, although the degree of the poisoning depends largely on the nature of catalysts and the kind of halides. For this reason, the reactions are often carried out in the presence of a base. The Rosenmund reduction involves the hydrogenolysis of acyl halides and has been employed extensively for the synthesis of aldehydes from carboxylic acids.[193] Various procedures other than catalytic hydrogenolysis are also available for dehalogenations, including reductions using chemical reagents, such as $LiAlH_4$, $NaBH_4$, R_3SnH, Zn/AcOH or Zn/EtOH, alkali metal/liquid NH_3, Sn(II) salts, and electrochemical reductions. As would be expected from the reactivities of halogens toward displacement reactions, catalytic hydrogenolysis of carbon–halogen bonds becomes difficult in the order C–I < C–Br < C–Cl < C–F, which is in line with the corresponding increasing bond energies [240 kJ (57.4 kcal)·mol^{-1} for C–I, 276 kJ (65.9 kcal)·mol^{-1} for C–Br, 328 kJ (78.5 kcal)·mol^{-1} for C–Cl, and 441 kJ (105.4 kcal)·mol^{-1} for C–F].[194] The ease of hydrogenolysis also depends greatly on the structural environment of the halogen atom in a molecule and is affected by the presence of other functional groups. The high reactivity of an allyl- or benzyl-type halogen is particularly noted.

13.4.1 R–X Bonds at Saturated Carbons

Baltzly and Phillips studied the hydrogenolysis of various halogen compounds using Pd–C and Adams platinum as catalysts.[195] Aliphatically bound halogens are quite resistant to hydrogenolysis in acid or neutral conditions unless activated by adjacent unsaturation. Thus, isobutyl bromide, *t*-butyl bromide, *t*-amyl bromide, phenethyl bromide, and cyclohexyl bromide are not hydrogenolyzed in methyl or ethyl alcohol at room temperature and low hydrogen pressure. Ethyl 3-bomopropionate and monochloroacetic acid also retained their halogens. On the other hand, ethyl dichloroacetate and trichloroacetic acid were susceptible to hydrogenolysis. The bromine of ethyl bromoacetate was removed quantitatively, although less rapidly than the bromine of bromobenzene.

Bases are added frequently as promoters in catalytic dehalogenations to neutralize the liberated halogen acid that may inhibit the action of catalyst.[196] Denton et al. studied the effects of added potassium acetate to the rates of hydrogenolysis of various halogen compounds with a Pd–C as catalyst in methanol (Table 13.8).[196]

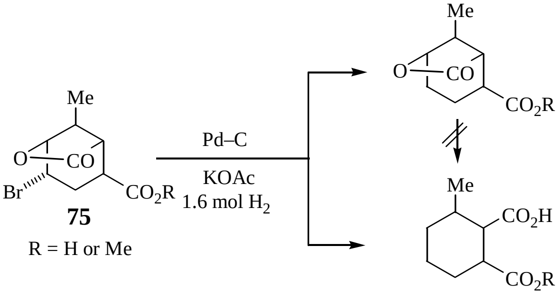
Heptyl bromide was not hydrogenolyzed whatsoever, even in the presence of potassium acetate, while phenethyl bromide and 3-phenylpropyl bromide were hydogenolyzed at considerable rates with addition of the base. Ethyl 3-bromopropionate, which resisted hydrogenolysis in neutral alcohol, as mentioned above, was hydrogenolyzed in the presence of the base, although at a slow rate. It is seen that the bomine located at the α-position is markedly activated by electron-withdrawing benzoyl and ethoxycarbonyl groups.

TABLE 13.8 Effects of Added Potassium Acetate on the Rates of Hydrogenolysis of Halogen Compounds[a,b]

	Initial Rate (ml H_2·min^{-1}·mg cat^{-1}) × 10^3	
Compound	In MeOH	In MeOH with KOAc (1 equiv.)
n-$C_7H_{15}Br$	Nil	Nil
PhCl	10	75
PhBr	79	125
$Ph(CH_2)_2Cl$	Nil	2.5
$Ph(CH_2)_2Br$	6.5	25
$Ph(CH_2)_3Br$	7.5	17
$PhCOCH_2Br$	122	165
EtO_2CCH_2Br	11	68
$EtO_2C(CH_2)_2Br$	4	10

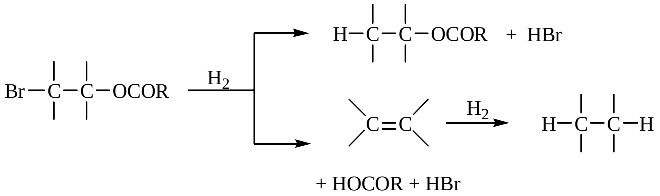
[a]Data of Denton, D. A.; McQuillin, F. J.; Simpson, P. L. *J. Chem. Soc.* **1964**, 5535. Reprinted with permission from Royal Society of Chemistry.
[b]The halogen compound was hydrogenated over Pd–C in 5 × 10^{-2}*M* solution at room temperature and atmospheric pressure.

The hydrogenolysis of certain α-bromolactones such as **75** proceeded only in the presence of potassium acetate, and it has been observed that elimination of the lactonic group may accompany the debromination, leading to formation of two products as shown in eq. 13.104. The results with other α-bromolactones supported the view that loss of the lactone group occurred through an elimination to give an olefinc intermediate that might or might not be hydrogenated further, as shown in Scheme 13.16.

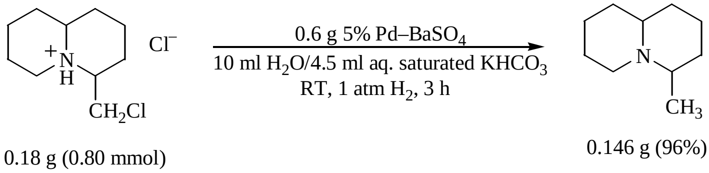


(13.104)

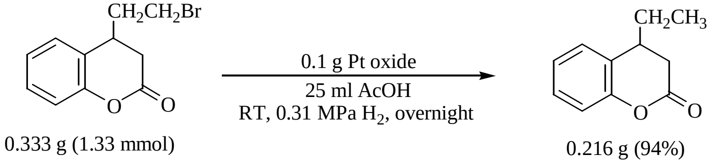
Dehalogenations at saturated carbons are seen quite commonly with cyclic compounds of the type RCH_2X. Equations 13.105,[197] 13.106,[198] and 13.107[199] are examples of such dechlorination, debromination, and deiodination, respectively, using palladium or platinum as catalyst. Equations 13.108[200] and 13.109[201] are those using Raney Ni.



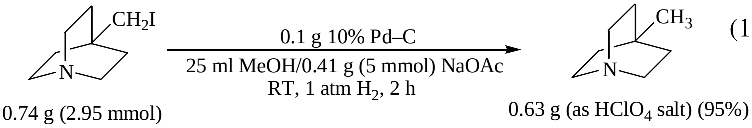
Scheme 13.16 Hydrogenolysis pathways of α-bromolactones in the presence of Pd–C and KOAc.



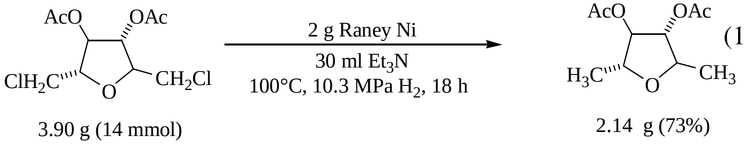
(13.105)



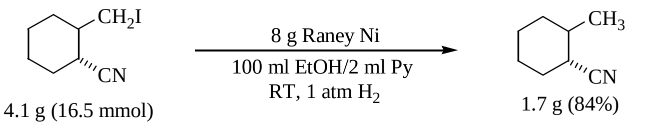
(13.106)



(13.107)

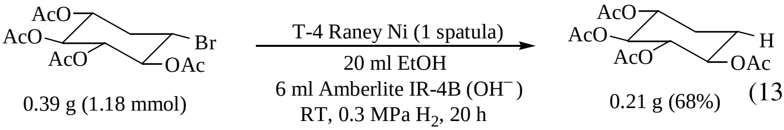


(13.108)



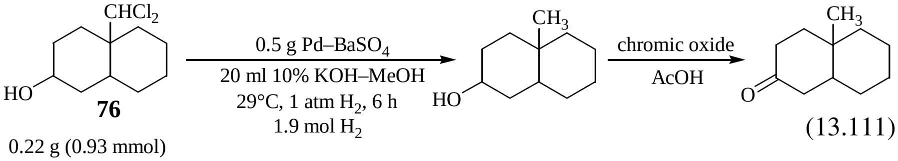
(13.109)

Raney Ni has also been used for removal of a secondary bromine, and has been applied for the synthesis of deoxy cyclitols with addition of Amberlite IR-4B anion-exchange resin to bind the liberated acid[202–205] (eq. 13.110[204]).



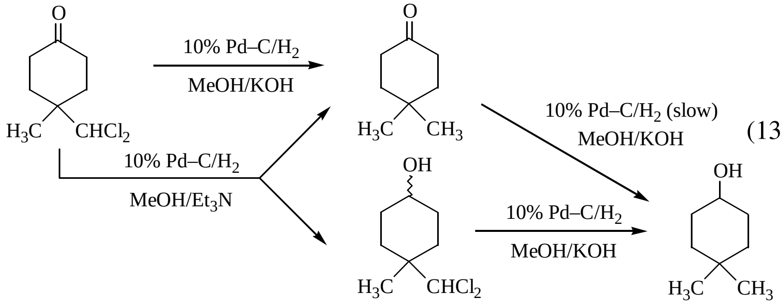
(13.110)

Woodward was successful to remove both the chlorine atoms of 10-dichloromethyl-2-hydroxydecahydronaphthalene (**76**) in the hydrogenation over Pd–$BaSO_4$ in 10% alcoholic potassium hydroxide, with formation of the corresponding methyl derivative, which was transformed into 10-methyl-2-decalone on oxidation with chromate mixture (eq. 13.111).[206]



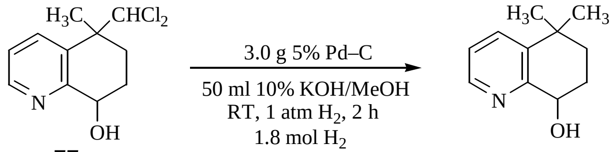
(13.111)

Reinecke compared the effects of two bases, potassium hydroxide and triethylamine, on the dehalogenation of dichlormethyl-substituted cyclohexanones over 10% Pd–C in methanol.[207] Dehalogenation of 4-dichloromethyl-4-methylcyclohexanone proceeded smoothly in the presence of potassium hydroxide to give primarily 4,4-dimethylcyclohexanone, while in the presence of triethylamine, in addition to 4,4-dimethylcyclohexanone and a little partially dechlorinated material, an approximately equal amount of stereoisomeric 4-dichloromethyl-4-methylcyclohexanols was isolated. Since the dichloro alcohols were rapidly dehalgenated to 4,4-dimethylcyclohexanol in the presence of potassium hydroxide, the inertia of the chlorine atoms in the dichloro alcohols was considered to be due to the presence of triethylamine (eq. 13.112).



(13.112)

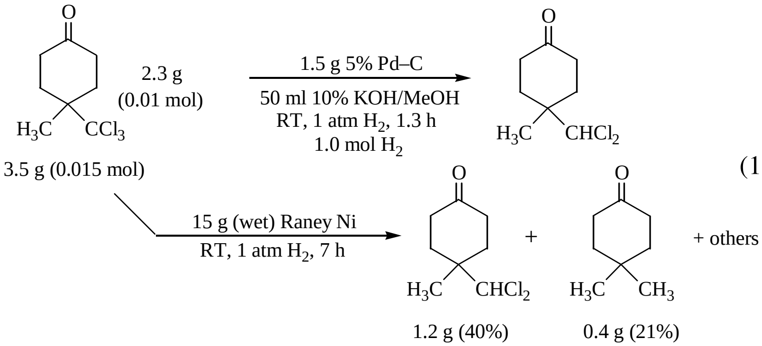
Isogai observed that 5-dichloromethyl-5-methyl-8-hydroxy-5,6,7,8-tetrahydroquinoline (**77**) was dehalogenated to give the 5,5-dimethyl derivative over 5% Pd–C in the presence of 10% methanolic potassium hydroxide (eq. 13.113).[208] On the other hand, 4-dichlormethyl-4-methylcyclohexanone did not absorb any hydrogen under the same conditions, in disagreement with the results due to Reinecke described above. Over a large excess amount of Raney Ni at room temperature and atmospheric hydrogen pressure, the dichloro ketone absorbed 1 equiv of hydrogen only to give the corresponding alcohol, thus resisting dehalogenation.



77
1.2 g (5 mmol)

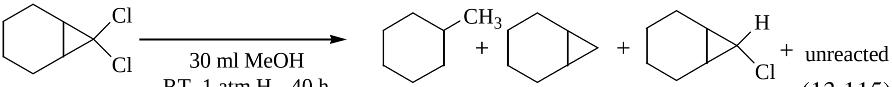
(13.113)

4-Trichloromethyl-4-methylcyclohexanone was dechlorinated to the dichloro derivative over Pd–C in 10% KOH–MeOH, while, with a large excess amount of Raney Ni a mixture of the dichloro derivative and the 4,4-dimethyl derivative was obtained together with small amounts of other unidentified products (eq. 13.114).[208]



(13.114)

Dechlorination of 7,7-dichloronorcarane (7,7-dichlorobicyclo[4.1.0]heptane) (**78**) with Raney Ni is accompanied by the rupture of the cyclopropane ring to give methylcyclohexane.[209] Isogai et al. studied in details the dehalogenation products of **78** over nickel catalysts in methanol in the absence or presence of potassium hydroxide under ordinary conditions (eq. 13.115).[210]



78

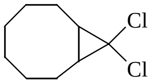
(13.115)

Catalyst	KOH			*Trans*	*Cis*	
U-Ni-B, 2 g Ni	—	Trace	Trace	3%	82%	15%
U-Ni-B, 2 g Ni	2 g	10%	5%	23	62	—
Raney Ni, 2.5 g	2	15	2	34	49	—
U-Ni-A, 2 g Ni	2	7	trace	9	62	—

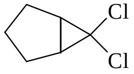
Over Urushibara Ni B (U-Ni-B) the reaction proceeded even in the absence of base and *cis*-7-chloronorcarane was formed selectively in an 82% yield. In the presence of

potassium hydroxide, the formation of methylcyclohexane and *trans*-7-chloronorcarane increased over any of the nickel catalysts employed. Over palladium and rhodium catalysts, **78** did not react to any appreciable extent. The stereochemistry of the formation of 7-chloronorcarane has been found to depend on the nature of the bases employed.[211] Over Raney Ni (W-5), the *cis* isomer was produced in large excess in the presence of ethylamine, diethylamine, triethylamine, and piperidine (*cis*:*trans* = 95:5), while formation of the *trans* isomer increased in the presence of ethylenediamine, trimethylenediamine, and hexamethylenediamine, the same as in the presence of alkali hydroxide. In the presence of ethylenediamine, apparently any hydrogen uptake was not observed; rather some hydrogen was evolved with formation of a Ni(II) complex, indicating a very strong interaction of Raney Ni with the diamine.

The effects of bases for 9,9-dichlorobicyclo[6.1.0]nonane (**79**) were similar as for **78**. However, the *trans*-monochlorocyclopropane derivatives were formed in greater amounts than the *cis* isomers from 6,6-dichlorobicyclo[3.1.0]hexane (**80**) and 2-oxa-7,7-dichlorobicyclo[4.1.0]heptane (**81**) in the presence of ethylenediamine.



79



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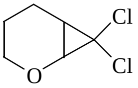
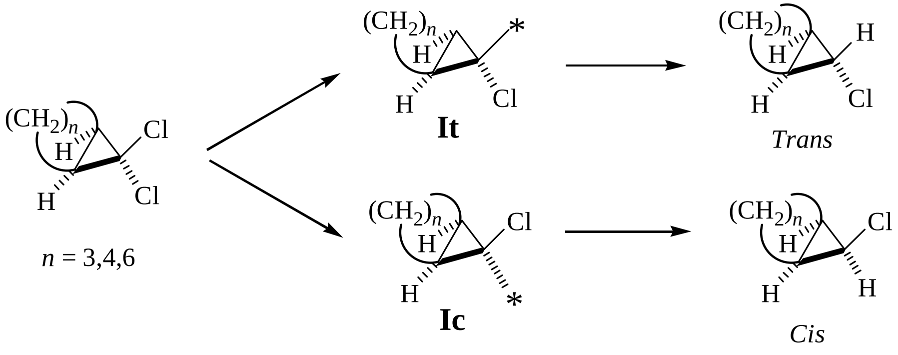


81

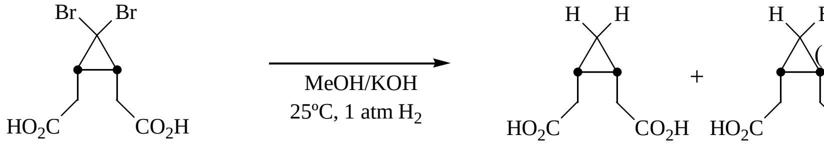
Selective formation of *cis*-monochlorocyclopropanes in the absence of base or in the presence of monoamines has been explained by preferential homolytic cleavage of a less hindered C–Cl linkage to form the more stable surface intermediate **Ic** rather than the less stable **It** under the circumstances that the substrate can be strongly adsorbed. On the other hand, in the presence of an alkali hydroxide or a diamine, which may be adsorbed strongly to the catalyst, it is probable that the substrate is adsorbed weakly and formation of the more stable *trans*-monochlorocyclopropanes increases with an increased contribution of a nucleophilic reaction (Scheme 13.17).[211]

3,3-Dibromocyclopropane-*cis*-1,2-diacetic acid (**82**) is debrominated to the corresponding cyclopropane derivative over Raney Ni in the presence of alkali and to the



Scheme 13.17 Stereochemistry of the dechlorination of bicyclic *gem*-dichlorocyclopropanes.

monobromo derivative over platinum or palladium catalysts, without accompanying ring opening (eq. 13.116).[212]



(13.116)

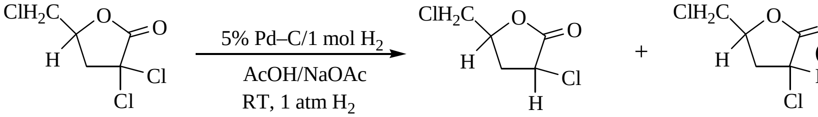
82

3.2 g (0.01 mol)	0.2 g Pt oxide, 300 ml MeOH 4 g KOH, 24 h		1.22 g (51%)
15.3 g (0.048 mol)	Raney Ni (2 teaspoons), 200 ml MeOH, 12.8 g KOH in 50 ml H_2O, 24 h	6.4 g (84%)	

13.4.2 Activated Alkyl and Cycloalkyl Halides

A halogen atom may be activated toward hydrogenolysis by an electron-withdrawing group located alpha to the halogen. Thus, the halogens in compounds such as α-haloketones, α-halonitriles, α-haloacids, α-haloesters, and α-halosulfonyl compounds are hydrogenolyzed more readily than those in the corresponding compounds lacking such functional groups.

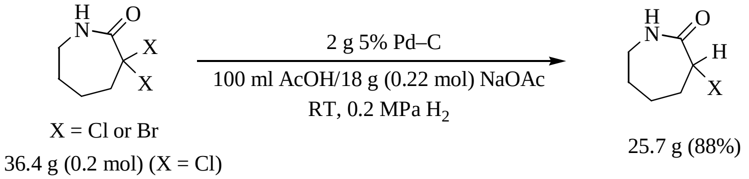
According to Baltzly and Phillips, ethyl bromoacetate is hydrogenolyzed quantitatively over Pd–C in methanol, although ethyl β-bromopropionate and monochloroacetic acid resisted dehalogenation. Dehalogenation of di- and trichloroacetic acid proceeded to the monochloroacetic acid stage in aqueous or aqueous alcoholic solutions. In absolute alcohol, however, trichloroacetic acid and its ester lost only a little over 1 mol of halogen, and the reduction of dichloroacetic acid was also incomplete, probably because of poisoning by the hydrogen chloride produced when absolute alcohol was the solvent.[195] α-*gem*-Dichlorolactone **83** is readily hydrogenolyzed to give the monochloro derivative over 5% Pd–C in acetic acid in the presence of sodium acetate, and a chloromethyl group remains intact (eq. 13.117).[213]



(13.117)

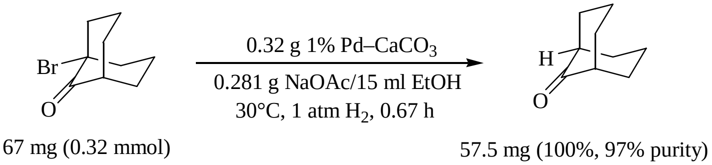
83 | 30–40% | 40–45%

In the course of the synthesis of DL-lysine from ε-caprolactam, Wineman et al. obtained 3-chloro- and 3-bromo-2-oxohexamethyleneimine in high yields by hydrogenolysis of the corresponding *gem*-dihaloimines, obtained by halogenation of ε-caprolactam, over 5% Pd–C in acetic acid containing sodium acetate (eq. 13.118).[214] The reaction with the dibromoimine proceeded much faster than in the case of the dichloroimine, and 3-bromo-2-oxohexamethyleneimine was obtained in a 94.8% yield.



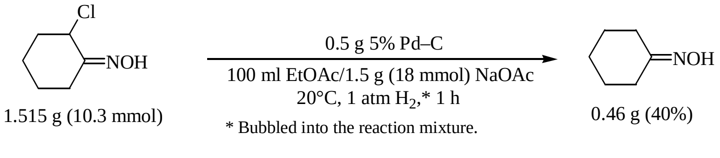
(13.118)

α-Bromoketones are readily debrominated with palladium catalyst without reduction of the carbonyl group. For example, 1-bromobicyclo[3.3.1]nonan-9-one is quantitatively debrominated over 1% Pd–$CaCO_3$ in ethanol in the presence of sodium acetate without reduction of the carbonyl function (eq. 13.119).[215] Phenacyl chloride was rapidly hydrogenolyzed to give ethylbenzene. It is probable that the chlorine atom had been lost prior to the hydrogenation and hydrogenolysis of the carbonyl group.[195] The rates of debromination of phenacyl bromide greatly increased in the presence of potassium acetate (see Table 13.8).[196]



(13.119)

α-Halooximes can be dehalgenated to the oximes without affecting the hydroxyimino group. 2-Chlorocyclohexanone oxime was dechlorinated to give cyclohexanone oxime by hydrogenolysis over 5% Pd–C in ethyl acetate containing sodium acetate (eq. 13.120).[216] Similarly, various α-chlorocycloalkanone oximes were converted to the corresponding oximes in 66–89% yields over Pd–C in methanol without addition of base.[217]

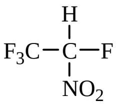


(13.120)

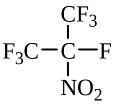
Selective dechlorination of α-chlorooximes over palladium catalyst was also achieved in an acidic medium.[218] 2-Chlorocyclohexanone oxime as sulfate or in the presence of 1 equivalent of sulfuric acid was hydrogenated over 10% Pd–C in acetic acid to give 84.5% of cyclohexanone oxime.[218c]

2-Chlorocyclododeca-5,9-dien-1-one oxime, obtained by treatment of *trans*, *trans*,*cis*-1,5,9-cyclododecatriene with NOCl in HCl-saturated CCl_4, was converted to cyclododecanone oxime in 90% yield, along with the formation of ~5% of cyclododecylamine, over Pd–Al_2O_3 in methanol at up to 60°C and atmospheric hydrogen pressure,[219] or over 5% Pd–$BaSO_4$ in methanol at room temperature and atmospheric pressure in 89% yield.[220] Similarly, 2-chlorocyclododecanone oxime was transformed into cyclododecanone oxime in 90% yield. With platinum catalyst, the chlorooxime

can be hydrogenated to give mainly cyclododecylamine.[217,220] In contrast, hydrogenation of α-chlorooximes resulting from 1,5-cyclooctadiene over palladium or platinum catalysts afforded a mixture of cyclooctanone oxime and cyclooctanone, along with cyclooctylamine, cyclooctylidenecyclooctylamine, and a trace amount of α-aminoethylcyclohexane.[220]



84

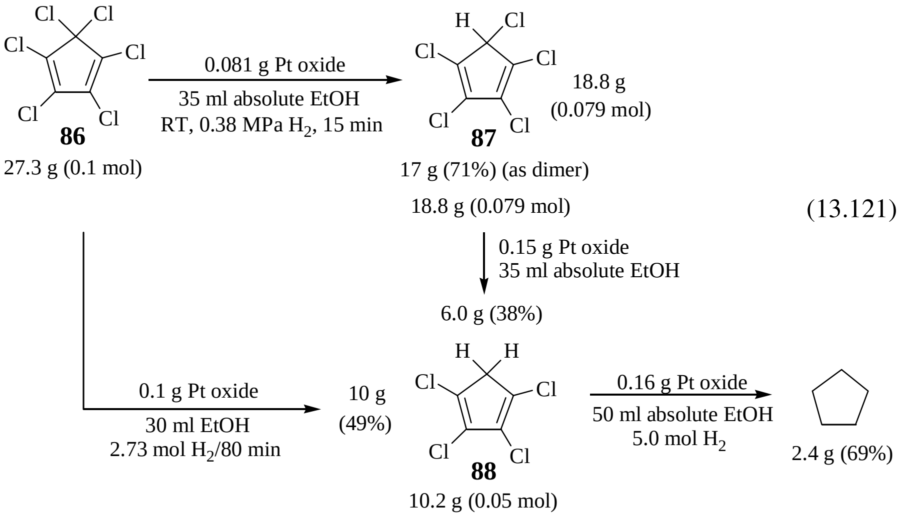


85

The α-fluoro atom activated by a nitro group in polyfluoro compounds such as **84** and **85** was removed on hydrogenation to the hydroxyimio compounds over a palladium black in methanol.[221]

13.4.3 Allyl and Vinyl Halides

Allyl and vinyl halides are highly reactive toward hydrogenolysis, and it is usually difficult to hydrogenate the unsaturated bonds without dehalogenation, even with fluoro compounds. Hexachlorocyclopentadiene **86** is dechlorinated stepwise over platinum oxide in ethanol; the allylic chlorine atoms are first removed. Pentachlorocyclopentadiene **87** and tetrachloropentadiene **88** were obtained in 71 and 49% yields after absorption of 1 and 2 equivs of hydrogen, respectively. The tetrachloro derivative **88** was also obtained by hydrogenation of **87**. Further hydrogenation of **88** gave cyclopentane in 69% yield (eq. 13.121).These results clearly indicate that allylic chlorines are much more reactive than vinylic chlorines, and they are readily removed prior to saturation of the double bonds.[222]



(13.121)

Hydrogenation of 1,3-dichloropropene (**89**) over platinum metals in cyclohexane at 100°C and 2.7–4.1 MPa H_2 was accompanied by extensive hydrogenolysis.[223] The proportion of hydrogenolysis increased in the following order: 5% Rh–Al_2O_3 < 5% Pd–Al_2O_3 < 5% Pt–Al_2O_3 (eq. 13.122). With 5% Ru–Al_2O_3, no reaction occurred. Over 5% Rh–Al_2O_3, which gave the least amounts of hydrogenolysis products, the vinylic chlorine was hydrogenolyzed even more extensively than the allylic chlorine (eq. 13.123).

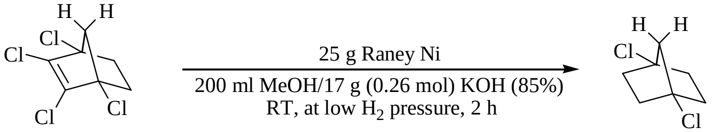
$$\underset{\textbf{89}}{ClHC{=}CHCH_2Cl} \xrightarrow[\substack{C_6H_{12} \\ 100°C,\ 2.7\text{–}4.1\ MPa\ H_2}]{\text{catalyst}} Cl(CH_2)_3Cl + CH_3CH_2CH_2Cl \qquad (13.122)$$

Catalyst	$Cl(CH_2)_3Cl$	$CH_3CH_2CH_2Cl$
5% Rh–Al_2O_3	47.9%	35.4%
5% Pd–Al_2O_3	19.2	33.3
5% Pt–Al_2O_3	6.1	32.2

$$CH_3CH{=}CHCl \xrightarrow{42.4\%} CH_3CH_2CH_2Cl \xleftarrow{57.8\%} CH_2{=}CHCH_2Cl \qquad (13.123)$$

(5% Rh–Al_2O_3, C_6H_{12}, 100°C, 4.0–4.3 MPa H_2)

The bridgehead chlorines in 1,2,3,4-tetrachloronorbornene (**90**) are not removed, although they are allylic; in the hydrogenation over Raney Ni in methanol in the presence of potassium hydroxide, only the vinylic chlorines are lost to give 1,4-dichloronorbornane (eq. 13.124).[224]

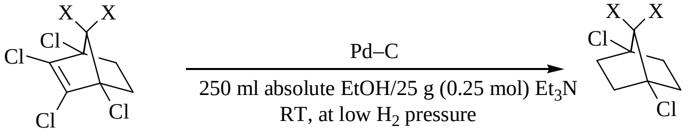


90
25 g (0.11 mol)

15 g (82%)

(13.124)

Similarly, 1,2,3,4,7,7-hexachloronorbornene (**91**, X = Cl) and 1,2,3,4-tetrachloro-7,7-dimethoxynorbornene (**91**, X = OMe) are hydrogenated without losing the allylic chlorines in the hydrogenation over Pd–C in ethanol in the presence of triethylamine; only the vinylic chlorines are removed (eq. 13.125).[225] The 7,7 bridge chlorines of the product may be further reduced to 1,4-dichloronorbornane by diphenyltin dihydride in diglyme at 110–120°C.

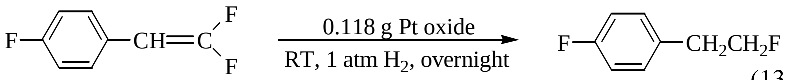


91 (X = Cl)
30.1 g (0.10 mol)

86%
(84% with X = OMe)

(13.125)

Hydrogenation of the trifluorostyrene **92** over platinum oxide results in partial defluorination during saturation of the side chain (eq. 13.126).[226]



92
1.40 g (8.9 mmol)

(13.126)

13.4.4 Benzyl and Aryl Halides

The halogens in benzyl halides are among the most reactive functions toward hydrogenolysis, in the same way as they are toward nucleophilic substitutions. Palladium appears to be the most active catalyst of the transition metals for the benzyl derivatives. The rates of hydrogenolysis often decrease with conversion, which might be due to inhibition by the toluene[227] or hydrogen halide produced.[196] The effects of solvents and additives on the rate of hydrogenolysis have been studied with benzyl chloride at room temperature and atmospheric pressure, using 5% Pd–C, 5% Pt–C, and 5% Rh–C as catalysts (Table 13.9).[228] It is seen that 5% Pd–C is definitely more active than 5% Pt–C or 5% Rh–C, irrespective of the solvents used. The greatest rates were obtained in ethyl acetate, ethyl acetate with perchloric acid, and acetic acid with sodium acetate.

Dehalogenation of benzyl chloride over Raney Ni may result in the formation of either toluene or dibenzyl (1,2-diphenylethane).[229] For example, heating 10 g of benzyl chloride with 20 g Raney Ni in 100 ml of boiling methanol for 4 h gave 0.6 g dibenzyl and 2.6 g toluene. When the amount of Raney Ni was reduced to 10 g, the amount of dibenzyl increased to 1.1 g, while with 40 g Ni the amount of toluene increased to 5 g (70%). Under the same conditions, but in the presence of 1 equiv of potassium hy-

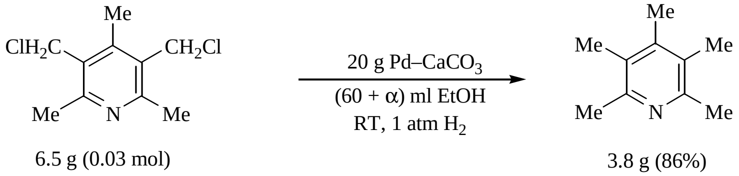
TABLE 13.9 Effects of Media on the Rate of Hydrogenolysis of Benzyl Chloride over Pd–C, Pt–C, and Rh–C Catalysts[a,b]

	Average Rate to 50% Completion[c] ($ml\ H_2 \cdot min^{-1}$)		
Solvent	5% Pd–C	5% Pt–C	5% Rh–C
H_2O	40	10	4
$H_2O + HClO_4$ (1%)	60	15	6
EtOAc	100	4	2
EtOAc + $HClO_4$ (1%)	120	6	5
AcOH	50	5	5
AcOH + NaOAc	120	40	16
MeOH	40	30	15
n-C_6H_{14}	20	1	0

[a]Data of Southwick, A. in Rylander, P. N. *Catalytic Hydrogenation over Platinum Metals*; Academic Press: New York, 1967; p 406. Reprinted with permission from Academic Press Inc.
[b]Benzyl chloride (4.5 ml) was hydrogenated over 0.5 g of 5% metal–C in 100 ml solvent at room temperature and atmospheric pressure.
[c]Except very slow reductions.

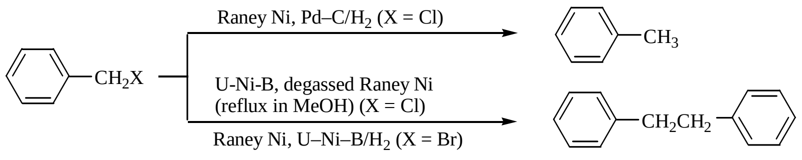
droxide and 10 g Ni, 0.75 g dibenzyl and 1.5 g toluene were obtained with a considerable amount of benzyl chloride remaining unchanged. The formation of dibenzyl disappears almost completely in the cold, in the presence of alkali, and with an external supply of hydrogen. Isogai found that, although hydrogenation of benzyl chloride over Raney Ni or 5% Pd–C in methanol in the presence of sodium hydroxide afforded toluene predominantly with formation of dibenzyl at a very low level, over Urushibara Ni B (U-Ni-B), dibenzyl was formed in far greater amounts, and, in contrast to with Raney Ni, the amounts of dibenzyl formed increased with increasing amounts of U-Ni-B employed.[230] By refluxing with U-Ni-B or degassed Raney Ni in methanol, dibenzyl was formed almost exclusively. Dibenzyl is formed more selectively with benzyl bromide than with benzyl chloride. Thus, when benzyl bromide was hydrogenated over U-Ni-B, the greater part of the product was dibenzyl. Even in the hydrogenation over W-4 Raney Ni, dibenzyl was formed in a greater amount than toluene (Scheme 13.18).[230] The benzylic fluorines of *o*- and *m*-trifluoromethylbenzoic acids were hydrogenolyzed by treatment with Raney Ni or Raney Co alloy and alkali to give the corresponding toluic acids in high yields.[231]

α-Chlorine atoms in *N*-heterocyclic aromatics are also reactive toward hydrogenolysis. An excellent application is seen in the synthesis of pentamethylpyridine by hydrogenolysis of 3,5-bis(chloromethyl)-γ-collidine over Pd–C in ethanol at room temperature and atmospheric pressure (eq 13.127).[232]



(13.127)

The halogens on aromatic rings may also be susceptible to hydrogenolysis, the ease of which, however, depends largely on the nature of halogen, catalyst, and solvent, as well as the presence or absence of other functional groups. Usually, the hydrogenolysis is promoted by the presence of base. Hasbrouck compared the rates of hydrogenolysis of chlorobenzene over 5% Pd–C, 5% Pt–C, and 5% Rh–C in acetic acid, acetic acid–sodium acetate, ethanol, and ethanol–sodium hydroxide at room temperature and atmospheric pressure (Table 13.10).[233] It is seen that 5% Pd–C is the most active catalyst in each solvent, especially in the presence of the bases.



Scheme 13.18 Formation of dibenzyl from benzyl halides over Ni catalysts.

Bromobenzene is hydrogenolyzed in a much greater rate than chlorobenzene over Pd–C in methanol. The rates are further increased by added potassium acetate for both bromo- and chlorobenzenes.[196] In one patent, sodium phosphate was used as an effective base in the dechlorination of 4,6-dichloro-2-nitroresorcinol to 2-aminoresorcinol over Pd–C.[234]

The halogens on aromatic rings may be activated by an electron-withdrawing group located at the *ortho* and *para* positions. *p*-Fluorobenzoic acid, as its sodium salt in an aqueous solution, was hydrogenolyzed to give benzoic acid and then more slowly converted to cyclohexanecarboxylic acid over platinum catalyst.[235] With Raney Ni or Raney Co alloy and alkali, it was also defluorinated.[231]

Dehalogenation tends to occur during the hydrogenation of halonitrobenzenes to haloaminobenzenes (Section 9.3.2). In the hydrogenation of *p*-chloronitrobenzene in ethanol at room temperature and atmospheric pressure, the degree of dechlorination increased in the order 5% Rh–C (2%) < 5% Pt–C (23%) < 5% Pd–C (53%) at the uptake of 3 equiv of hydrogen.[236]

The nuclear hydrogenation of haloaromatic compounds is usually accompanied by complete loss of halogen, and only a few cases are known where the corresponding saturated halo compounds were obtained. Hydrogenation of *o*-fluorophenylphosphonic acid over 5% Rh–Al_2O_3 in ethanol affords hydrogen fluoride and pure cyclohexylphosphonic acid with uptake of 4 mol of hydrogen. Similarly, hydrogenation of *m*-chlorophenylphosphonic acid gave cyclohexylphosphonic acid and hydrogen chloride. Apparently, hydrogenation of the aromatic ring and dechlorination proceeded at comparable rates, since only 0.29 mol of hydrogen chloride had been formed when the reduction was interrupted after absorption of 1 mol of hydrogen per mole of *m*-chlorophenylposphonic acid.[237] Under similar conditions the hydrogenation of *p*-bromo- and *o*-iodophenylphosphonic acids stopped at earlier stages of hydrogenation, since the catalyst was strongly poisoned by the hydrogen bromide and the hydrogen iodide formed, respectively. On the other hand, the hydrogenation of chlorobenzene over 5% Rh–C in methanol gave a mixture of cyclohexane and chlorocyclohexane.[238]

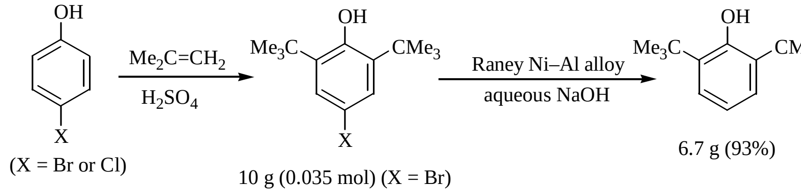
Hart and Cassis, Jr. utilized the dechlorination with Raney alloy and alkali in the synthesis of 2,6-di-*t*-butylphenol from 4-bromo- or 4-chlorophenol as starting mate-

TABLE 13.10 Rates of Hydrogenolysis of Chlorobenzene[a,b]

Catalyst	AcOH	AcOH/NaOAc	EtOH	EtOH/NaOH
5% Pd–C	4	55	25	100
5% Pt–C	3	45	5	8
5% Ph–C	1	11	7	4

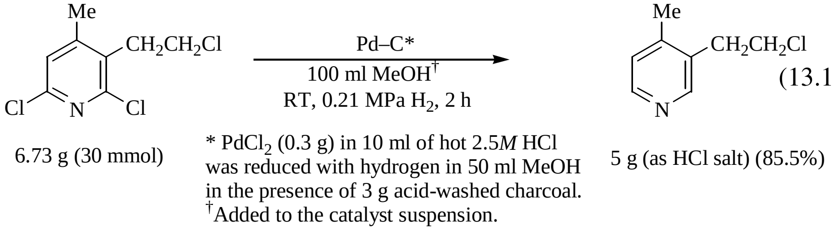
[a]Hasbrouck, L. in Rylander, P. N. *Catalytic Hydrogenation over Platinum Metals*; Academic Press: New York, 1967; p 406. Reprinted with permission from Academic Press Inc.
[b]Average rates to 30% completion (except for the slowest reductions) in ml $H_2 \cdot min^{-1}$. Chlorobenzene (5.3 g, 0.0476 mol) was hydrogenated over 0.5 g 5% metal–C in 50 ml solvent in the presence of 0.1 mol of base (if used) at room temperature and atmospheric hydrogen pressure. Over Pt and Rh catalysts in AcOH/NaOAc, the hydrogenation continued at a slow rate after theoretical absorption for complete hydrogenolysis.

rial (eq. 13.128).[239] Hydrogenolysis over palladium catalyst resulted in the formation of 2,6-di-*t*-butylcyclohexanone.

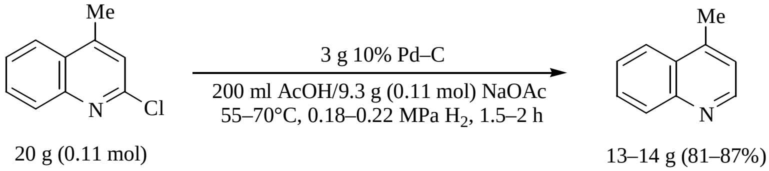


(13.128)

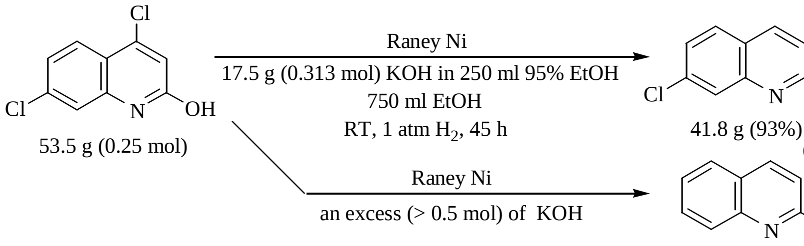
The nuclear-substituted halogens of aromatic *N*-hetereocycles may also be susceptible to hydrogenolysis. In particular, those at the 2 and 6 positions of pyridines and at the 2 and 4 positions of quinolines are readily hydrogenolyzed, as shown in eqs. 13.129–13.131. In the example shown in eq. 13.131, it was noticed that the rate of hydrogenolysis of the 4-chlorine was considerably greater than that of the 7-chlorine in the presence of an excess of alkali, and the selective dechlorination of the 4-chlorine was successful in an alcoholic solution containing 1.25 equiv of potassium hydroxide at room temperature and atmospheric pressure.[240]



(13.129)[241]



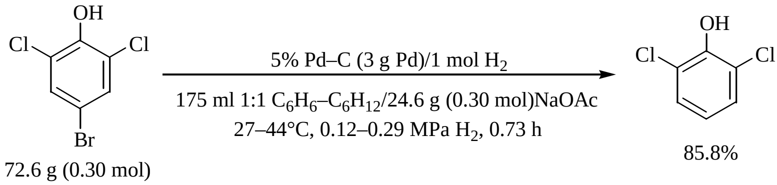
(13.130)[242]



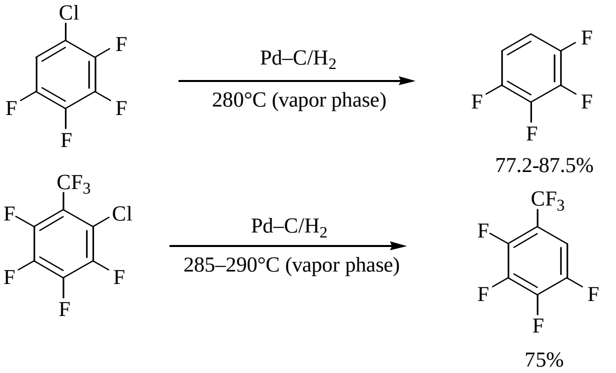
(13.131)

Polyhalo aromatic compounds with different halogens may be selectively hydrogenolyzed, usually in the order of increasing ease of hydrogenolysis: fluorine < chlorine < bromine < iodine. Thus, 4-bromo-2,6-dichlorophenol was selectively debrominated to give 2,6-dichlorophenol over palladium catalyst in benzene–cyclo-

hexane containing sodium acetate with uptake of 1 equiv of hydrogen (eq. 13.132).[243] The examples in eq. 13.133 show that only the chlorine can be removed selectively from chloropolyfluoro aromatic hydrocarbons over Pd–C in a vapor-phase hydrogenation at 280–290°C.[244]



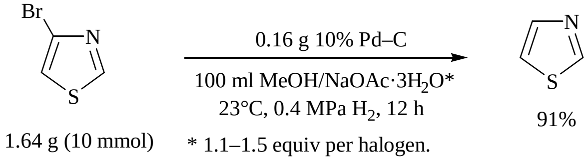
(13.132)



(13.133)

13.4.5 Halothiazoles

Kerdesky and Seif studied the catalytic dehalogenation of various halothiazoles.[245] They found 10% Pd–C to be superior to Raney Ni, 5% Pt–C, palladium black, and 5% Rh–C in achieving this hydrogenolysis. 4-Halothiazoles were effectively hydrogenolyzed over 10% Pd–C, but unsuccessful with Raney Ni, although Erlenmeyer et al. dehalogenated 2- and 5-bromothiazoles with use of Raney Ni.[246,247] An example is given in eq 13.134 for the dehalogenation of 4-bromothiazole over 10% Pd–C. Hydrogenolysis with the other catalysts afforded yields of less than 50%.



(13.134)

Bromothiazoles were more reactive than their chloro analogs. For example, 2,4-dibromo-5-(hydroxymethyl)thiazole was completely debrominated to give 5-(hydroxymethyl)thiazole in 94% yield at 23°C for 12 h, while the corresponding dichloro analog gave only 28% yield of 5-(hydroxymethyl)thiazole even at 60°C for 60 h; the major product was 4-chloro-5-(hydroxymethyl)thiazole (63%).

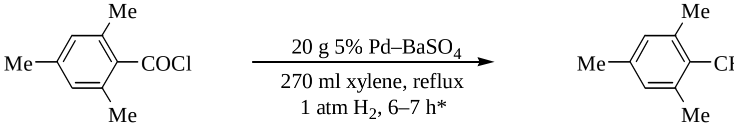
13.4.6 Hydrogenolysis of Acid Chlorides to Aldehydes (the Rosenmund Reduction)

The catalytic hydrogenolysis of acid chlorides to aldehydes over Pd–$BaSO_4$ has been widely utilized in organic synthesis and is known as the *Rosenmund reduction*.[248–250] For depressing the hydrogenation of aldehydes to alcohols and other products, the catalyst is usually poisoned by a sulfur-containing material such as quinoline-S, thioquinanthrene, phenylisothiocyanate, or thiourea. Quinoline–S is prepared by refluxing freshly distilled quinoline (6 g) with sulfur (1 g) for 5 h. After cooling, the quinoline-S is diluted to 70 ml with xylene.[251,252] The solution thus prepared contains 0.1 g of quinoline–S per milliliter, and 0.01 g of quinoline-S is usually employed for 1 g of the catalyst. The reduction is conveniently carried out by bubbling hydrogen gas into a hot or refluxing solution of an acid chloride in an aromatic hydrocarbon such as xylene, toluene, or benzene at atmospheric pressure. Reduction at a reduced pressure favors the removal of hydrogen chloride and also allows the reaction to be carried out at lower temperature. The extent of reduction can be monitored by determining the amount of hydrogen chloride evolved. An appropriate apparatus for the Rosenmund reduction has been described by Zymalkowski.[253]

The reduction may be accompanied by side reactions such as ester, acid, or acid anhydride formation, which result from overreduction of aldehydes to alcohols or to hydrocarbons and water (eq. 13.135). The hydrogen to be used should be dry and contain no oxygen.

$$\begin{array}{lcl} \mathrm{RCHO} \xrightarrow{H_2} \mathrm{RCH_2OH} & \xrightarrow{H_2} & \mathrm{RCH_3 + H_2O} \\ \mathrm{RCOCl + RCH_2OH} & \longrightarrow & \mathrm{RCO_2CH_2R + HCl} \\ \mathrm{RCOCl + H_2O} & \longrightarrow & \mathrm{RCO_2H + HCl} \\ \mathrm{RCOCl + RCO_2H} & \longrightarrow & \mathrm{(RCO)_2O + HCl} \end{array} \qquad (13.135)$$

Affrossman and Thomson studied the effect of poisoning by some sulfur-containing compounds in the reduction of benzoyl chloride to benzaldehyde over 5% Pd–$BaSO_4$ in toluene at 110°C.[254] Tetramethylthiourea was found to be the most effective in preventing hydrogenation beyond the aldehyde stage among the poisons investigated: tetramethylthiourea, thiourea, thiophene, and dibenzothiophene. Weygand and Meusel obtained almost quantitative yields (96%) of benzaldehyde by reduction of benzoyl chloride (3 g) over platinum oxide (0.1 g) poisoned by thiourea (7–10 mg) in refluxing toluene (10 ml) for 6–12 h.[255] In some cases good results are obtained without an added catalyst poison, as in an example shown in eq. 13.136,[256] although the

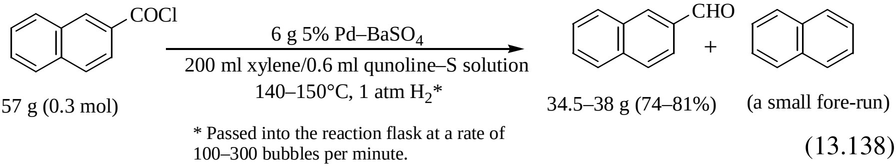


(13.136)

90 g (0.49 mol) * With stirring; 18 h with no stirrer. 53–60 g (70–80%)

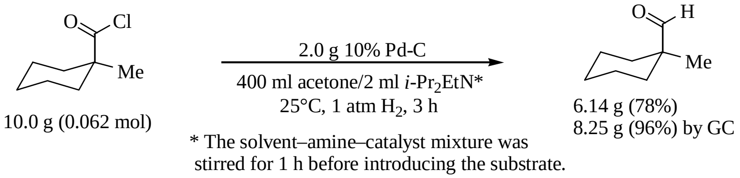
solvent may have contained enough impurities to act as a catalyst poison when used without purification.[257] Decarbonylation may accompany the reduction (eq. 13.137), as observed, for example, in the reduction of *p*-anisoyl,[258] 3,4,5-trimethoxybenzoyl,[259] and 2-naphthoyl chlorides (eq. 13.138).[252]

$$\mathrm{RCOCl + H_2 \longrightarrow RH + CO + HCl} \qquad (13.137)$$

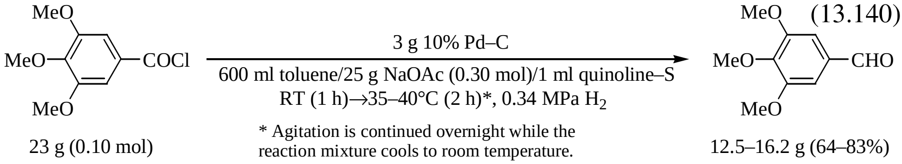


(13.138)

The reduction of acid chlorides may proceed at lower temperatures in the presence of a tertiary amine or sodium acetate. Peters and van Bekkum improved the method of Sakurai and Tanabe,[260] using ethyldiisopropylamine, instead of *N*,*N*-dimethylaniline, as a HCl acceptor.[261] Ethyldiisopropylamine had the advantage of forming an acetone soluble hydrochloride, and workup of the reaction mixture was easier when acetone was used as solvent. Reductions in the presence of these basic substances have been found to be especially effective when the acid chlorides are labile to decarbonylation. Examples of the use of base are shown in eqs. 13.139[261] and 13.140.[262] When the original procedure of the Rosenmund reduction was applied to 1-*t*-butylcyclohexanecarbonyl chloride, *t*-butylcyclohexane was the sole product, compared to greater than 95% yield of the corresponding aldehyde in the presence of ethyldiisopropylamine or sodium acetate.[261]



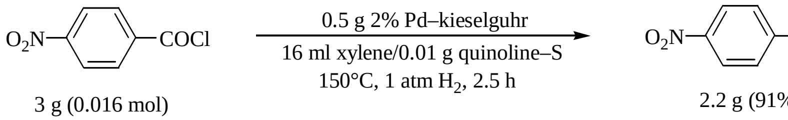
(13.139)



(13.140)

Many examples have been described in the literature where selective transformation of acid chlorides to aldehydes was successful in the presence of other functional groups. Cinnamoyl chloride was transformed to cinnamaldehyde in 54–60% yields over Pd–$BaSO_4$ with addition of quinoline–S or thioquinanthrene.[263] *o*-Chlorobenzoyl chloride gave *o*-chlorobenzaldehyde in 70% yield in reduction over 2% Pd–kieselguhr in toluene in the presence of quinoline–S.[249] Similarly, 4-chloro- and

6-chloro-1-naphthoyl chlorides were converted to the corresponding aldehydes over 5% Pd–$BaSO_4$ in 75 and 63.6% yields, based on the starting acid and the ester, respectively.[264] The acid chlorides of 4,6-dichloro- and 5,6-dichloropyridine-3-carboxylic acids and of 2,6-dichloropyridine-4-carboxylic acid were reduced to the corresponding aldehydes over unpoisoned Pd–$BaSO_4$ in xylene in 50–60% yield based on the acids.[265] *p*-Nitrobenzoyl chloride was converted to *p*-nitrobenzaldehyde in 91% yield without affecting the nitro group (eq. 13.141).[249] Similarly, *p*-cyanobenzoyl chloride was reduced to *p*-cyanobenzaldehyde in 63% yield over quinoline–S-poisoned 5% Pd–$BaSO_4$ in xylene.[266]



(13.141)

With some dibasic acids, the yields of the corresponding dialdehydes were unsatisfactory. For example, the reduction of succinyl dichloride[267] and phthaloyl dichloride[268,269] gave, respectively, γ-butyrolactone and phthalide as major products. With *m*- and *p*-phthalic dichlorides, however, the corresponding dialdehydes were obtained in 83 and 81% yields, respectively.

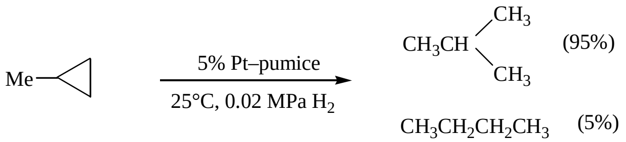
13.5 HYDROGENOLYSIS OF CARBON–CARBON BONDS

In general, the catalytic hydrogenolysis of carbon–carbon linkages in saturated compounds takes place only under rather drastic conditions, as in an industrial process known as *hydrocracking*, where heavy oils are transformed into gasoline or light fuel oils at 200–400°C and 1–10 MPa H_2, such as over zeolites loaded with noble metals or other transition metals.[270] In a commercial process known as *hydrodealkylation*, even more drastic conditions are used for the production of benzene or naphthalene from their alkylated derivatives, using, for example, Cr_2O_3–Al_2O_3 as catalyst.[271] However, in the cases where carbon–carbon linkages are activated, for example, by ring strain and/or unsaturation, the cleavage may occur under much milder conditions.

13.5.1 Cyclopropanes

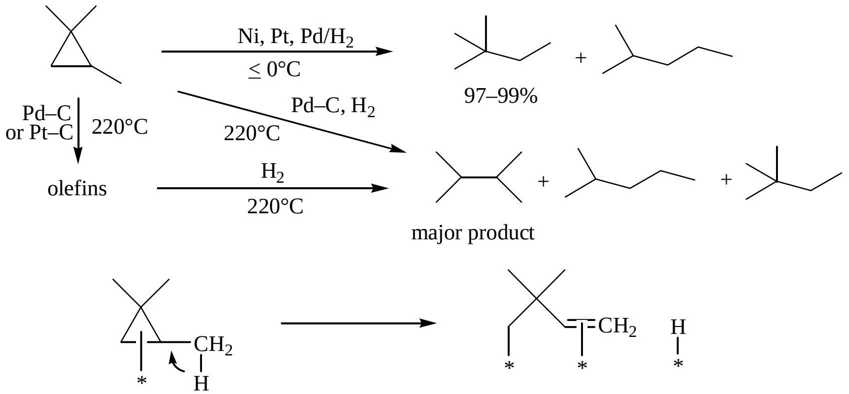
Because of the ring strain, together with a π-character of the cyclopropane ring, the activation energies for the hydrogenolysis of cyclopropane rings are much lower than those for other saturated carbon–carbon bonds. Accordingly, the ring cleavage of cyclopropanes with hydrogen may take place under very mild conditions.[272] The vapor-phase hydrogenolysis of cyclopropane over silica-supported platinum metals has been studied by Dalla Betta et al. at −35–80°C and hydrogen and cyclopropane pressures of 0.020 and 0.0030 MPa, respectively.[273] The order of the specific activities based on the unit surface area of the metals compared at −10°C was Rh > Pt > Pd > Ir > Os > Ru. Osmium and ruthenium were the only catalysts that showed the activities for the cyclopropane fragmentation reaction to methane and ethane besides the simple ring-

opening reaction. Monoalkyl- and 1,1-dialkylcyclopropanes are cleaved at the bond opposite the substituted carbon. Thus, hydrogenolysis of methylcyclopropane over a platinum catalyst at 25°C occurs mainly at the C2–C3 linkage to give isobutane (eq. 13.142).[274] At higher temperatures, however, different selectivities may result from occurrence of prior isomerization to butenes.



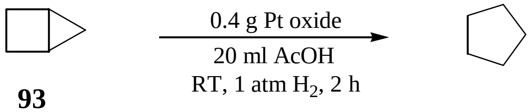
(13.142)

Deuterolysis of 1,1-dimethylcyclopropane on platinum, nickel, palladium, and rhodium films at low temperatures gives neopentane almost exclusively; the formation of isopentane is less than 1% of the product.[275] Similarly, in other polyalkylcyclopropanes as well, the bond between the two least substituted carbons tends to be cleaved. For example, deuterolysis of 1,1,2-trimethylcyclopropane at low temperatures (≤ 0°C) affords neohexane almost exclusively (97–99%).[276] At higher temperatures, however, different products may be formed as a result of prior isomerization. Thus, over Pd–C at 220°C 1,1,2-trimethylcyclopropane yields 2,3-dimethylbutane as the major product along with 2-methylpentane and neohexane.[277] The mixed olefins formed by passage of the cyclopropane over Pt–C or Pd–C at 220°C similarly gave 2,3-dimethylcyclohexane and 2-methylpentane by hydrogenation (Scheme 13.19).[278] From the observations by Prudhomme and Gault, that the deuteroneohexanes formed by deuterolysis on platinum at 0°C contained ~60% of d_3–d_6 species and on palladium more than 80% of d_5 and d_6 species,[276] Augustine and Patel have suggested that deuterolysis of 1,1,2-trimethylcycopropane proceeds through an adsorbed olefinic precursor which is expected to be formed by the adsorption of the C2–C3 bond most readily accessible to the catalyst surface, as shown in Scheme 13.19.[279] Bicy-



Scheme 13.19 Products and mechanism of the hydrogenolysis of 1,1,2-trimethylcyclopropane.

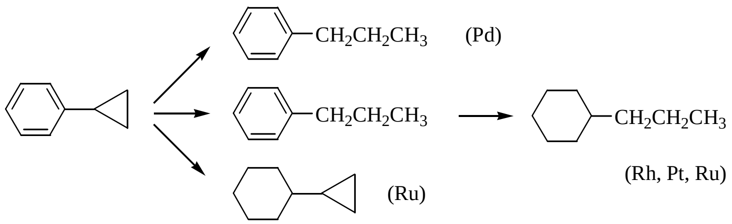
clo[2.1.0]pentane (**93**) is readily hydrogenolyzed to give cyclopentane over platinum oxide in acetic acid at room temperature, indicating that hydrogenolysis took place at the most strained linkage of the cyclopropane ring (eq. 13.143).[280] It is noted that the heat of hydrogenolysis for **93** [55 kcal (230 kJ)·mol^{-1}] is 28 kcal (117 kJ)·mol^{-1} greater than that for the hydrogenation of the isomeric cyclopentene [27 kcal (113 kJ)·mol^{-1}].[281]



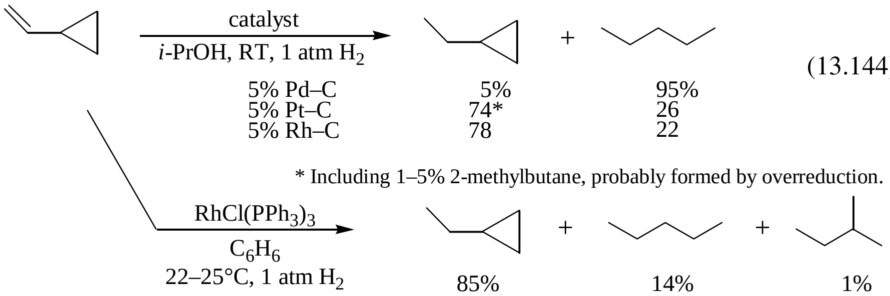
93
3.1 g (0.046 mol)

(13.143)

Unsaturated groups on the cyclopropane ring may have a great effect on the ease and the position of the ring cleavage, which depend on the nature of catalysts. Hydrogenolysis of phenylcyclopropane over palladium catalyst gives propylbenzene selectively.[282,283] Phenylcyclopropane is hydrogenolyzed 90 times more rapidly over palladium than over platinum,[282] as might be expected from the high activity of palladium catalyst for the hydrogenation of a conjugated system, which would also be the case in the benzene and cyclopropane ring system. In ethanol at 30°C and 1 atm H_2, Pd–C was more active for the hydrogenolysis than were any of Rh–C, Pt–C and Ru–C catalysts, affording propylbenzene quantitatively. Hydrogenolysis over Rh–C and Pt–C gave approximately 80% of propylbenzene, which was further hydrogenated to give propylcyclohexane. Over Ru–C, hydrogenation of the benzene ring to give cyclopropylcyclohexane occurred competitively with the hydrogenolysis of the cyclopropane ring to give propylbenzene, affording a mixture of 75% of propylcyclohexane and 25% of cyclopropylcyclohexane ultimately (Scheme 13.20). Apparently, cyclopropylcyclohexane was not hydrogenolyzed or was hydrogenolyzed only slowly under these conditions. Vinylcyclopropane is hydrogenolyzed predominantly at the C1–C2 linkage to give pentane over 5% Pd–C in isopropyl alcohol at room temperature. On the other hand, over 5% Pt–C and 5% Rh–C, hydrogenation of the double bond to give ethylcyclopropane becomes predominant.[284] It is noteworthy that hydrogenation with Wilkinson's rhodium complex leads largely to the hydrogenation product (eq. 13.144).[285]

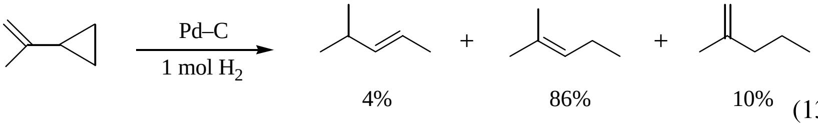


Scheme 13.20 Hydrogenolysis of phenylcyclopropane over platinum metal catalysts.



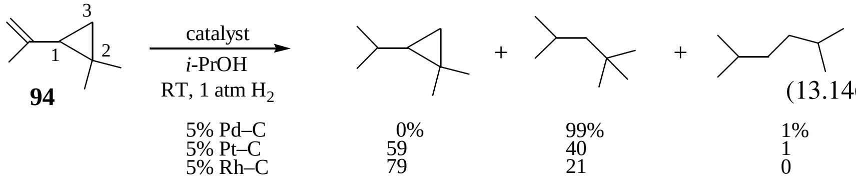
(13.144)

When hydrogenation of isopropenylcyclopropane over palladium catalyst is interrupted at the uptake of 1 equiv of hydrogen, a mixture of olefinic intermediates is obtained in high yield (eq. 13.145), indicating that the adsorption of isopropenylcyclopropane on palladium catalyst is so much stronger than the olefinic intermediates as to prevent their hydrogenation.[286]



(13.145)

Hydrogenation of 1-isopropenyl-2,2-dimethylcyclopropane (**94**) over 5% Pd–C gives the ring-opened products only, while over 5% Pt–C and 5% Rh–C, the hydrogenation of the isopropenyl group occurs predominantly to give 1-isopropyl-2,2-dimethylcyclopropane as the main product (eq. 13.146).[284]

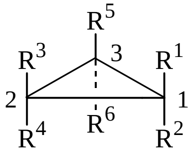


(13.146)

Schultz studied the hydrogenolysis of cyclopropane derivatives bearing unsaturated groups directly on the three-membered ring, including ketones, acids, and esters, over a Pd–C catalyst in ethanol at room temperature and atmospheric pressure (Table 13.11).[287] All the cyclopropanes bearing an adjacent carbonyl groups preferentially undergo ring cleavage at the C1–C2 bond. In the case of the cyclopropyl methyl ketones, hydrogenolysis occurs exclusively at the C1–C2 bond (Nos. 1–9), while with the esters and acids more than 70% C1–C2 bond cleavage was observed (Nos. 10–18). In the compounds in which a benzene ring is the only unsaturated moiety in conjugation with the cyclopropane ring, exclusive cleavage of a carbon–carbon bond adjacent to the aromatic ring took place (Nos. 19–22 and 24–26), in accord with the results with phenylcyclopropane.

While the hydrogenation of cyclopropyl methyl ketone over Pd–C affords 2-pentanone quantitatively, over copper–barium–chromium oxide at 100°C and 10–14

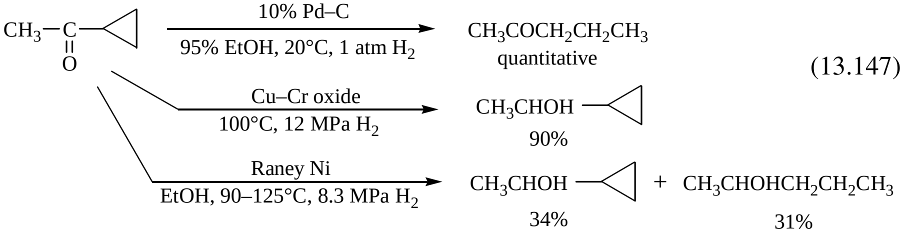
TABLE 13.11 The Effect of Substituents on the Position of Ring Opening in Hydrogenolysis of Substituted Cyclopropanes over Pd–C[a,b]



Entry No.	R^1	R^2	R^3	R^4	R^5	R^6	Bond Cleaved (%) C1–C2	C1–C3	C2–C3
1	COMe	H	H	H	H	H	50	50	
2	COMe	H	C_4H_8 H	ü‘9çûCç !24çû¤Hç!28ç4ç4Î,cé	H	c	50	50	
3	COMe	H	H	Ph	H	H	100	—	—
4	COMe	H	Me	Ph	H	H	100	—	—
5	COMe	Ph	H	Me	H	Me	50	50	—
6	COMe	Ph	Me	H	H	Me	50	50	—
7	COMe	Me	Ph	Ph	H	H	100	—	—
8	COMe	Me	H	Ph	H	H	100	—	—
9	COMe	H	Ph	Ph	H	H	100	—	—
10	CO_2Et	H	H	Ph	H	H	100	—	—
11	CO_2Me	Me	Ph	Ph	H	H	89	11	—
12	CO_2Me	Me	H	Ph	H	H	85	15	—
13	CO_2Me	H	Ph	Ph	H	H	80	—	20
14	CO_2H	H	H	Ph	H	H	100	—	—
15	CO_2H	H	Ph	Ph	H	H	100	—	—
16	CO_2H	Me	Ph	Ph	H	H	100	—	—
17	CO_2H	H	Ph	H	H	H	100	—	—
18	CO_2H	Me	H	Ph	H	H	70	30	—
19	CH_2OH	Me	Ph	Ph	H	H	100	—	—
20	CH_2OH	Me	H	Ph	H	H	—	—	100
21	CH_3CHOH	H	Ph	Ph	H	H	—	—	100
22	OAc	Ph	Ph	H	H	H	100[d]	—	—
23	OAc	Me	Me	Me	H	H		No reaction	
24	OAc	Me	H	Ph	H	H	—	—	100[d]
25	Ph	H	H	Ph	H	H	100	—	—
26	Me	Me	Ph	H	H	H	—	—	100

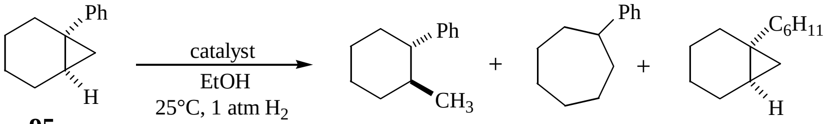
[a]Data of Schultz, A. L. *J. Org. Chem.* **1971**, *36*, 383. Reprinted with permission from American Chemical Society.
[b]Typically, 1 g of the cyclopropane was hydrogenated over 0.15 g of 10% Pd–C in 25 ml of 95% ethanol at room temperature and atmospheric pressure.
[c]A tetramethylene grouping bridges R^4 and R^6.

MPa H_2, 1-cyclopropylethanol was obtained in 90% yield. Over Raney Ni, a mixture of 1-cyclopropylethanol and 2-pentanol was formed (eq. 13.147).[288] Mitsui et al. studied the hydrogenolysis of 1-phenylbicyclo[4.1.0]heptane (**95**) over Raney Ni, palladium black, Pd–C, Rh–C, and platinum oxide in ethanol at 25°C and atmospheric hydrogen pressure (eq. 13.148).[289] Hydrogenolysis of **95** at the C1–C7 linkage gave



(13.147)

trans-1-phenyl-2-methylcyclohexane, the product hydrogenolyzed with retention of the configuration. Small amounts of phenylcycloheptane were also formed over the metals other than Raney Ni. Over rhodium and platinum catalysts the hydrogenation of the benzene ring to give 1-cyclohexylbicyclo[4.1.0]heptane took place concurrently.



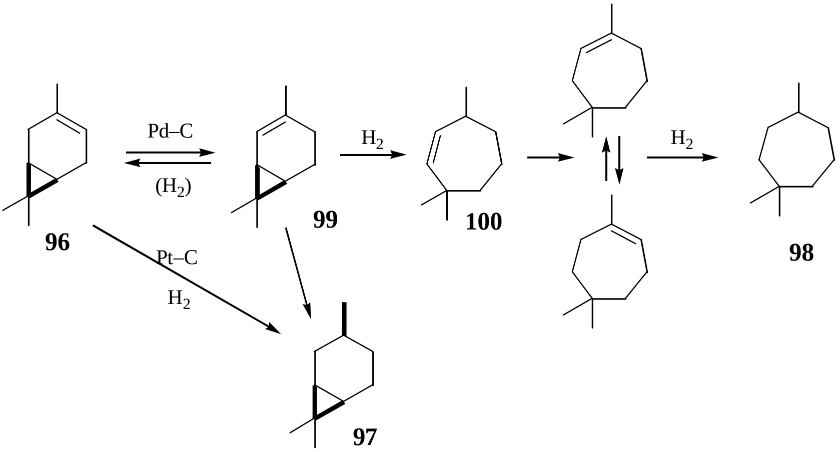
95

(13.148)

Raney Ni	100%	—	—
Pd–C	90	10%	—
$Pd(OH)_2$	95	4	—
Rh–C	60	10	30%
Pt oxide	15	5	80
Pt black	40	20	40

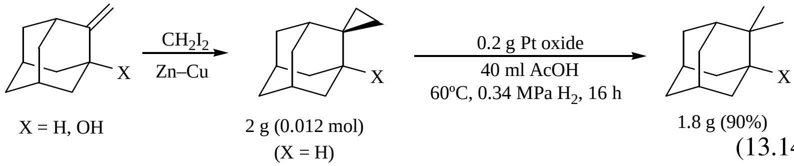
The hydrogenation of (+)-3-carene (**96**) over 5% Pd–C in ethanol or propionic acid gives a mixture of (–)-*cis*-carane (**97**) and 1,1,4-trimethylcycloheptane (**98**). At temperatures higher than 73°C in propionic acid, formation of **98** becomes quantitative. Over 5% Pt–C in ethanol at room temperature and 10 MPa H_2, *cis*-carane **97** was virtually the only product (98%).[290] Examination by GC of the course of the hydrogenation of **96** over Pd–C in ethanol showed that it rapidly equilibrated with (+)-2-carene (**99**). No equilibration takes place in the absence of hydrogen. Since **97** was unaffected under the conditions that quantitatively converted **96** to **98**, it has been suggested that the ring opening takes place by a 1,4 addition of hydrogen to the conjugated system of **99** to give 1,1,4-trimethyl-2-cycloheptene (**100**), which may isomerize rapidly to the more stable 3- and 4-ene isomers (Scheme 13.21).

The catalytic hydrogenolysis of cyclopropyl compounds, which are readily obtained by cyclopropanation of an olefinic bond, such as by the Simmons–Smith reaction (see eq. 13.149), has found useful synthetic applications for introducing isopropyl, *gem*-dimethyl, or angular methyl groups.[291] Examples are shown in eqs. 13.149–13.152. In the case shown in eq. 13.150, the stereoisomeric composition of the products as well as the results of deuteration indicated that the hydrogenolysis of the cyclopropane ring proceeded via prior isomerization to 10-methyl-$\Delta^{1,9}$-octalin.[292] In the compound in eq. 13.152, hydrogenolysis over platinum oxide in acetic acid took place to give mixtures, accompanied by the formation of a cyclooctane derivative and dehydroxylated products. However, use of rhodium–platinum oxide cleaved the cy-

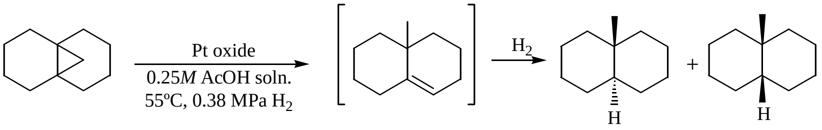


Scheme 13.21 Hydrogenation pathways of 3-carene over palladium and platinum catalysts.

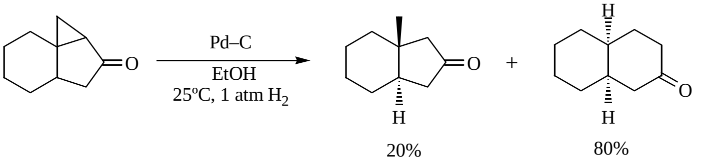
97



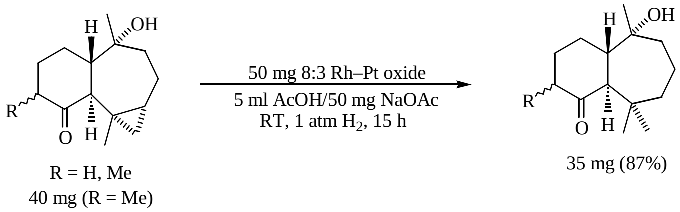
(13.149)[293]



51.5 : 48.5 (13.150)[294]



(13.151)[295]

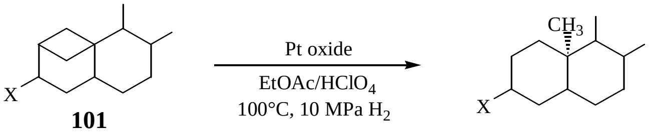


(13.152)[296]

clopropane ring in the desired direction, and the addition of sodium acetate depressed the hydrogenolysis of the tertiary hydroxyl group.

13.5.2 Cyclobutanes

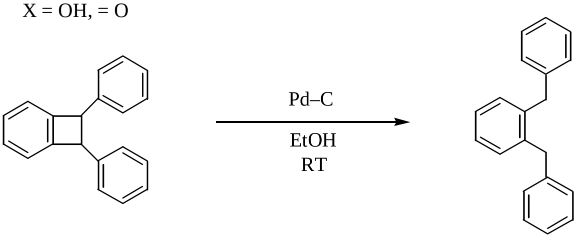
Cyclobutanes are much less susceptible to hydrogenolysis than cyclopropanes, except those compounds where the ring is highly strained or activated by accumulated phenyl groups. Cyclobutane is hydrogenolyzed to butane at a high temperature of 200°C over Ni–kieselguhr.[297] The bicyclic steroid **101** containing a cyclobutane ring is hydrogenolyzed to give a 10α-methyl derivative at 60–170°C over platinum oxide, ruthenium oxide, or 10% Pd–C (eq. 13.153).[298] 1,2-Diphenylbenzocyclobutene is readily hydrogenolyzed over Pd–C in ethanol at room temperature (eq. 13.154).[299] Under these conditions, however, benzocyclobutene is hydrogenolyzed only with difficulty.



101

X = OH, = O

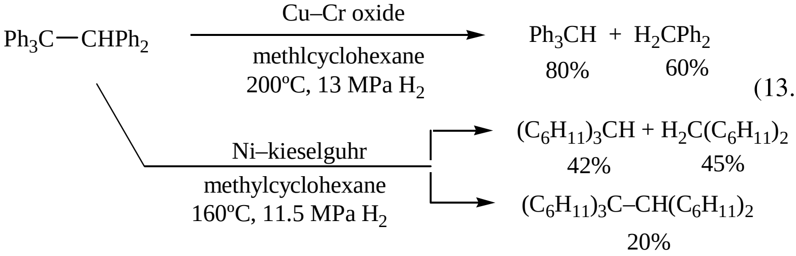
(13.153)



(13.154)

13.5.3 Open-Chain Carbon–Carbon Bonds

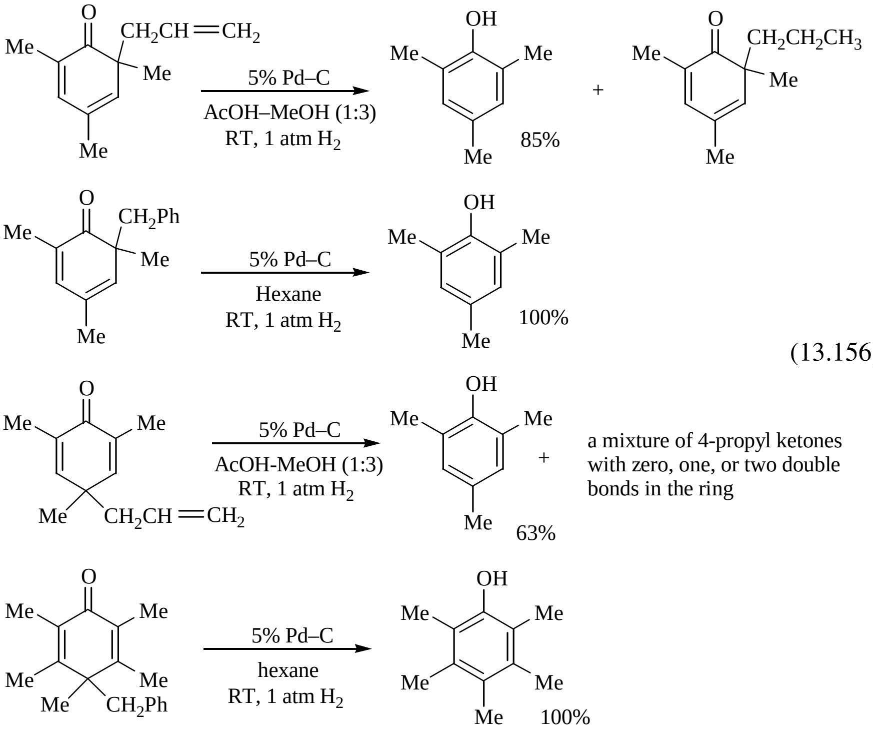
Unless under drastic conditions, an open chain carbon–carbon bond in saturated compounds seldom undergoes hydrogenolysis. However, the carbon–carbon bond may be labilized by multiply substituted phenyl groups. For example, pentaphenylethane and 1,1,2,2- and 1,1,1,2-tetraphenyethanes are hydrogenolyzed quantitatively over copper–chromium oxide at 200°C without affecting the benzene rings. Over Ni–kieselguhr at 160°C, the hydrogenolysis of pentaphenylethane competes with the hydrogenation of the benzene ring, leading to a mixture of tricyclohexylmethane, dicyclohexylmethane, and pentacyclohexylethane (eq. 13.155). Both 1,1,2,2- and



(13.155)

1,1,1,2-tetraphenylethane, however, are hydrogenated to the corresponding tetracyclohexylethanes without accompanying hydrogenolysis.[300] In a vapor-phase hydrogenation of toluene, xylene, and mesitylene over platinum catalyst, hydrogenolysis of the phenyl–methyl bond may accompany the hydrogenation of the aromatic ring competitively at 30–100°C. Over Pt–Coriglass catalyst at 76°C, the selectivity of the hydrogenolysis was 10.4% with toluene, 37.9% with *p*-xylene, and 43.8% with mesitylene, thus increasing with increasing number of methyl substituents. Selectivity decreases with increasing temperature. Thus, selectivity with toluene decreases from 23.1% at 53.5°C to 10.4% at 76.0°C.[301] Such a low-temperature hydrogenolysis of methyl-substituted benzenes does not occur over nickel, cobalt, and rhodium catalysts.[302] An S_N2 substitution mechanism in a π-adsorbed methylbenzene species has been proposed for the low-temperature hydrogenolysis.

The examples in eq. 13.156 show that the allyl- or benzyl-carbon bonds linked to the conjugated cyclohexadienone rings are hydrogenolyzed more readily than the alkyl–carbon bonds. The phenol drivatives are formed apparently by 1,8 (or 1,4) and 1,6 addition of hydrogen for the linearly and cross-conjugated systems, respectively. The percentage of hydrogenolysis in the allyl derivative increases with increasing polarity and increasing hydrogen bonding power of the solvent. No hydrogenolysis occurred with a 2,6-di-*t*-butylcyclohexadienone.[303]



(13.156)

The hydrogenation of primary alcohols over nickel catalysts may be susceptible to loss of the methlylol group (CH_2OH), affording the hydrocarbons with one carbon

atom less than the parent alcohols.[3] This reaction, called *reductive dehydroxymethylation*, can be expressed by the general formula shown in eq. 13.157 and is considered to proceed via formation of aldehyde followed by decarbonylation (eq. 13.158).[304]

$$RCH_2OH + 2H_2 \rightarrow RH + CH_4 + H_2O \qquad (13.157)$$

$$RCH_2OH \rightarrow RCHO \rightarrow RH + CO \rightarrow RH + CH_4 + H_2O \qquad (13.158)$$

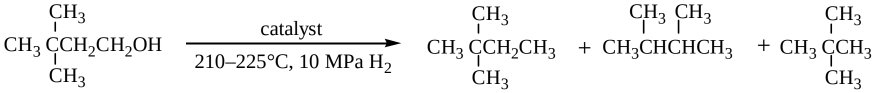
Over Raney Ni, primary alcohols are dehydroxymethylated at 250°C under 10–20 MPa H_2. The reaction proceeds smoothly where R = $C_{11}H_{23}$ (eq. 13.159), $C_{13}H_{27}$, $C_{17}H_{35}$, and *cy*-$C_6H_{11}CH_2CH_2$.[3]

$$\underset{37\text{ g }(0.2\text{ mol})}{C_{11}H_{23}CH_2OH} \xrightarrow[250°C,\ 10\text{–}20\text{ MPa }H_2,\ 5\text{ h}]{5\text{ g Raney Ni}} \underset{90\%}{C_{11}H_{24}} \qquad (13.159)$$

Secondary alcohols undergo carbon–oxygen cleavage rather than a carbon–carbon bond under the same conditions. For example, the hydrogenation of cyclohexanol and 2-octanol gives cyclohexane and octane, respectively, as the only hydrocarbons. The primary–secondary glycol octadecane-1,12-diol, $CH_3(CH_2)_5CHOH(CH_2)_{10}CH_2OH$, produces heptadecane, $C_{17}H_{36}$. If the hydroxyl groups in a glycol are in the 1,3 positions and, in addition, there are alkyl substituents in the 1, 2, or 3 positions, hydrogenolysis at the carbon–carbon bond becomes easier and occurs even over copper–chromium oxide under milder conditions.[305] For example, 2-methylpentane-2,4-diol was hydrogenolyzed within 30 min to give isopropyl alcohol in 86% yield, along with 13% of 4-methylpentan-2-ol, over copper–chromium oxide at 200°C and 17.5 MPa H_2 (eq. 13.160).[5]

$$\underset{59\text{ g }(0.5\text{ mol})}{(CH_3)_2COHCH_2CHOHCH_3} \xrightarrow[200°C,\ 17.5\text{ MPa }H_2,\ 0.5\text{ h}]{3\text{ g Cu–Cr oxide}} \begin{matrix} CH_3CHOHCH_3\ (86\%) \\ (CH_3)_2CHCH_2CHOHCH_3\ (13\%) \end{matrix} \qquad (13.160)$$

Ipatieff et al. studied the hydrogenolysis of various aliphatic and alicyclic alcohols in the presence of a Ni–Al_2O_3 catalyst at 210–225°C and 10 MPa H_2.[304] 3,3-Dimethyl-1-butanol yielded a mixture of 2,2-dimethylbutane and neopentane as the main products, while in the presence of either Ni–kieselguhr or Raney Ni, neopentane was formed in > 95% yields (eq. 13.161).



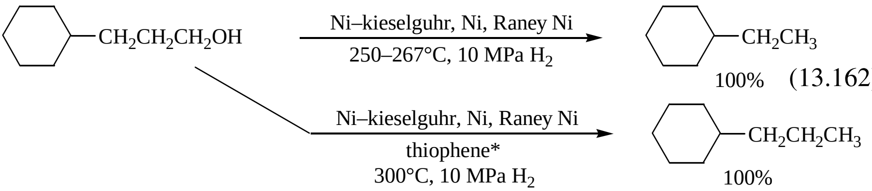
Catalyst	2,2-Dimethylbutane	2,3-Dimethylbutane	Neopentane
Ni–Al_2O_3*	35%	2%	24%†
Ni–kieselguhr			95
Raney Ni			97

(13.161)

* 76% conversion.
† The product contained also 25 mol% of isobutane.

Hydrogenolysis of cyclopentylmethanol, 1-cyclopentylethanol, 2-cyclopentylethanol, and cyclohexylmethanol over Ni–Al_2O_3 under the same conditions is accompanied by ring expansion or contraction. For example, in the case of cyclopentylmethanol a mixture of 70% of methylcyclopentane and 30% of cyclohexane was obtained. Thus, over Ni–Al_2O_3, the main reactions are the hydrogenolysis of the carbon–oxygen bond and an accompanying rearrangement, rather than dehydroxymethylation. On the other hand, the hydrogenation of 2-cyclopentylethanol, 1-methyl-1-hydroxymethylcyclohexane and 4-hydroxymethylcyclohexanol in the presence of Ni–kieselguhr at 190°C and 10 MPa H_2, gave the dehydroxymethylation products methylcyclopentane, methylcyclohexane, and cyclohexanol, respectively, in 80–100% yields.[306]

Pines et al. have found that the dehydroxymethylation of primary alcohols can be depressed by addition of small amounts of sulfur-containing compounds in the hydrogenations over Ni–kieselguhr, Raney Ni, or precipitated Ni, and the dehydroxylation (or accompanying isomerization) products result in high yields.[307] For example, the hydrogenation of 3-cyclohexyl-1-propanol over Ni–kieselguhr, Raney Ni, or precipitated Ni at 250–300°C in the absence of thiophene gave the dehydroxymethylation product, ethylcyclohexane, quantitatively, while in the presence of a small amount of thiophene at 300°C, only propylcyclohexane was formed (eq. 13.162).



(13.162)

* About 0.8 g of thiophene was added to 32 g of substrate and 3.2 g of catalyst.

In the case of 3,3-dimethyl-1-butanol and 1-methyl-1-hydroxymethylcyclohexane, the reductive dehydroxylation in the presence of thiophene was accompanied by a skeletal isomerization; 2,2- and 2,3-dimethylbutane were formed from the former alcohol and a mixture of ethylcyclohexane, methylcycloheptane, and 1,2-dimethylcyclohexane from the latter alcohol. It has been suggested that the sulfur compounds accentuate the acid properties of a nickel catalyst through their ability to poison the catalyst.

Primary 2-phenyl- or 2-(1-pyridyl)ethanols may undergo hydrogenolysis between the C1–C2 bond of the side chain on treatment with Raney Ni in refluxing ethanol.[308] Thus, 2-phenyl-1,2-propanediol yields ethylbenzene as a main product, along with lesser amounts of cumene and 2-phenyl-1-propanol (eq. 13.163). Similarly, 2-(1-pyridyl)ethanol gives 1-methylpyridine as the predominant product.

$$\underset{3\text{ g}}{\text{Ph}-\overset{\displaystyle CH_3}{\underset{\displaystyle OH}{C}}-CH_2OH} \xrightarrow[\substack{\text{50 ml absolute EtOH} \\ \text{reflux, 6 h}}]{\text{12 g Raney Ni}} \begin{array}{l} PhCH_2CH_3 \text{ (main product)} \\ PhCH(CH_3)CH_2OH \\ PhCH(CH_3)_2 \end{array} \qquad (13.163)$$

Primary alcohols with an aliphatic group on the β carbon, such as 2-cyclohexylethanol, gave only traces or none of the cleaved products, and the starting materials were recovered. Primary alcohols in which the aromatic nucleus is located on the γ carbon rather than the β carbon such as 3-phenyl-1-propanol also did not undergo significant hydrogenolysis.

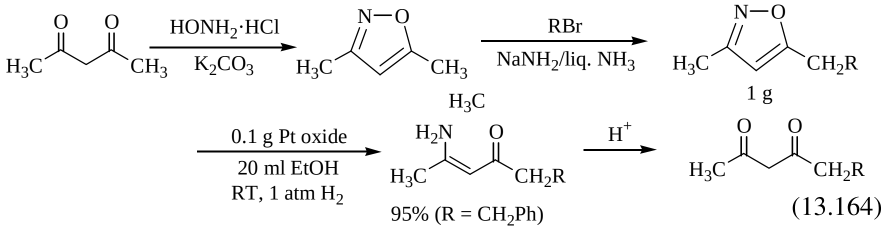
1,3-Diketones are known to be labile to cleavage of carbon–carbon linkages under rather mild conditions, as discussed in Section 5.3.3.

13.6 MISCELLANEOUS HYDROGENOLYSES

13.6.1 Nitrogen–Oxygen and Nitrogen–Nitrogen Bonds

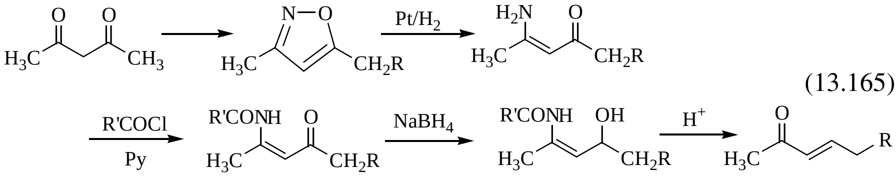
The hydrogenolysis of N–O linkages is involved in the hydrogenation of such groups as nitro, nitroso, hydroxyamino, oximino, or *N*-oxide to the corresponding amines. The facts that these groups are usually readily hydrogenated to amines indicate that the N–O linkages are hydrogenolyzed with ease (see Chapters 8 and 9).

An interesting example of the hydrogenolysis of an N–O linkage is the reductive ring opening of isoxazoles, which has been utilized in various syntheses. Isoxazoles are readily prepared by reaction of 1,3-diketones with hydroxylamine hydrochloride.[309] Since the 1,3-diketones may be regenerated by catalytic hydrogenolysis and subsequent hydrolysis,[310] the isoxazole ring formation can be used to protect the 1,3-diketone moiety during transforming the parent compound into its derivative. In an example shown in eq. 13.164, 3,5-dimethylisoxazole was alkylated regioselectively in the 5 position. Subsequent hydrogenolysis with platinum oxide in ethanol and hydrolysis gives γ-alkylated derivatives of the starting 1,3-diketone.[311]



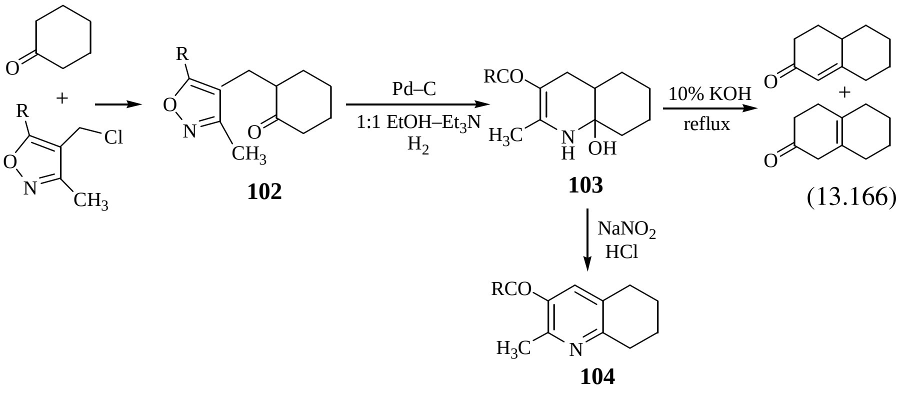
(13.164)

Kashima et al. utilized this reaction for the synthesis of α,β-unsaturated ketones from acetylacetone through a sequence of reactions described in eq. 13.165.[312]



(13.165)

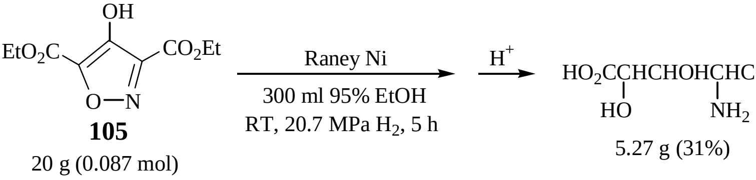
Stork et al. used Pd–C in 1:1 ethyl acetate and triethylamine for the hydrogenolysis of 2-(5-alkyl-3-methyl-4-isoxazolylmethyl)cyclohexanone (**102**), easily obtainable by reaction of cyclohexanone with 4-chloromethyl-5-alkyl-3-methylisoxazole, to give the cyclic vinylogous carbinolamide **103**.[313] By refluxing with 10% KOH, **103** (R = H) was transformed in high yield into the equilibrium mixture of $\Delta^{1,9}$- and $\Delta^{9,10}$-2-octalone.[313] Catalytic hydrogenolysis of **102**, R = Me, followed by treatment with sodium nitrite and hydrochloric acid gave 3-acetylpyridine derivative **104**, R = Me, in 64% yield[314] (eq. 13.166).



(13.166)

It was noted that the rate of hydrogenolysis of isoxazole rings over Pd–C was greatly affected by the pH of the medium. Although the isoxazole ring of **102**, R = H, was completely hydrogenolyzed with Pd–C in 1:1 ethyl acetate–triethylamine in 3 h, it was essentially unaffected in 5:1 ethyl acetate-acetic acid in 20 h.

Touster and Carter hydrogenolyzed an isoxazole to a β-amino alcohol over Raney Ni.[315] By hydrogenation of 3,5-diethoxycarbonyl-4-hydroxyisoxazole (**105**) over Raney Ni in ethanol at room temperature under high pressure, followed by hydrolysis, β,γ-dihydroxyglutamic acid was obtained (eq. 13.167).[315] The high activity of Raney Ni for the hydrogenolysis of fully substituted isoxazoles has also been noted by Stork et al.[316]



(13.167)

The hydrogenolysis of N–N linkages is involved in the hydrogenation of such compounds as hydrazines, azines, hydrazones, azo compounds, or azides. Usually, palladium, platinum, and nickel catalysts are used for the hydrogenolysis of these compounds (see Chapters 8 and 9). Palladium catalysts are known to be particularly effective for the hydrogenolysis of aromatic hydrazo compounds.[317]

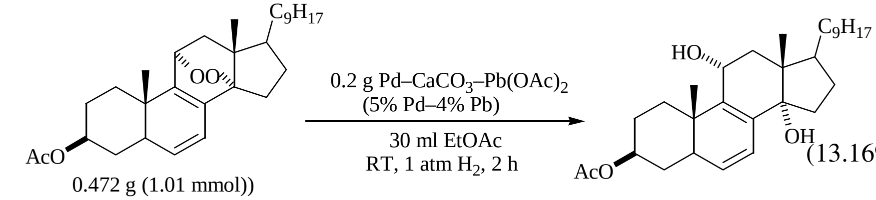
13.6.2 Oxygen–Oxygen Bonds

The hydrogenolysis of O–O linkages is involved in the hydrogenation of peroxides, hydroperoxides, and ozonides. Decomposition may occur catalytically in the absence of hydrogen, as was observed in as early as 1818 by Thénard with hydrogen peroxide in the presence of platinum.

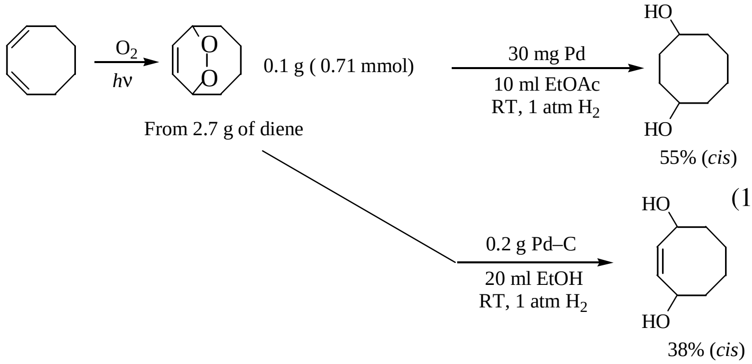
The hydrogenolysis of ozonides to aldehydes and ketones is not simple. Acids and other rearrangement products may be formed.[318] Pryde et al. studied the effect of solvent on the ozonization of methyl oleate and the reductive decomposition of the ozonolysis products.[319] The use of methanol resulted in superior yields of methyl azelaaldehydate as compared with nonreactive solvents. Although an 80% yield of azelaic semialdehyde, isolated as the semicarbazone, had been reported in the hydrogenation with Pd–$CaCO_3$,[320] hydrogenation in methanol with 10% Pd–C was accompanied by the formation of the dimethyl acetal. Conversion of the product to acetals gave 83% of pelargonaldehyde dimethyl acetal and 85% of methyl azelaaldehydate dimethyl acetal. The presence of pyridine during hydrogenation was found to reduce the amounts of dimethyl azelate, a major byproduct, and other byproducts, poisoned the catalyst for hydrogenation of olefinic unsaturation, and also prevented the acetal formation. The yield and purity of the aldehyde ester were thus improved, and unchanged methyl oleate could be recovered in the presence of pyridine (eq. 13.168)[321]

$$\underset{20.8\text{ g }(0.07\text{ mol})}{CH_3(CH_2)_7CH{=}CH(CH_2)_7CO_2Me} \xrightarrow[\substack{250\text{ ml MeOH}\\22.8\text{ g Py}}]{O_3} \xrightarrow[\text{RT, 1 atm }H_2,\ 1.7\text{ h}]{0.1\text{ g }10\%\text{ Pd–C}} \begin{matrix} CH_3(CH_2)_7CHO \\ 7.34\text{ g }(74\%)\ (82\%\text{ purity}) \\ OHC(CH_2)_7CO_2Me \\ 10\text{ g }(76\%)\ (88.7\%\text{ purity}) \end{matrix} \quad (13.168)$$

Hydrogenation of peroxides proceeds readily over palladium or platinum catalysts and provides a convenient method for the synthesis of glycols. Usually, hydrogenation of 1,4-peroxide bridge produces a *cis*-1,4-glycol.[322] Thus, hydrogenation of 1,3-cycloheptadiene peroxide over platinum oxide in ethanol gave the product consisting of at least 83% of *cis*-1,4-cycloheptanediol.[323] Use of Pd–$CaCO_3$ poisoned by lead acetate (Lindlar catalyst) is effective for hydrogenolysis of an unsaturated peroxide without affecting the olefinic bond, as in hydrogenation of an unsaturated steroid shown in eq. 13.169.[324,325] The peroxide of 1,3-cyclooctadiene may be hydrogenated either to the saturated *cis*-glycol over palladium black in ethyl acetate or to the unsaturated *cis*-glycol over Pd–C in ethanol (eq. 13.170).[326]



(13.169)



(13.170)

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